ANNUAL REPORT
OF
PROGRAM ACTIVITIES

NATIONAL HEART AND LUNG INSTITUTE

FISCAL YEAR 1972
PART I

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

U.S. NATIONAL HEART AND LUNG INSTITUTE

Fiscal Year 1972

PART I

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NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART AND LUNG INSTITUTE
July 1, 1971 to June 30, 1972
Office of the Director

During FY 1972 the National Heart and Lung Institute experienced a rewarding period of growth and expansion in its efforts to advance the health of the American people.

The problem of heart, blood, and lung diseases is a public health concern commanding the attention of every American. It is a costly problem running into billions of dollars a year, and it is exceedingly wasteful of human resources, amounting to the loss of more than one million lives per year and disabling many more of our citizens every year, year after year.

The National Heart and Lung Institute seeks to strengthen the control of heart, blood, and lung diseases by conducting, fostering, and supporting research, investigations, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of these diseases:

(i) By research initiated and performed in its own laboratories in Bethesda;

(ii) By investigator-initiated research supported through research grants to scientific institutions and individuals throughout the country and in some cases in other countries;

(iii) By initiating collaborative projects in targeted research areas in response to national needs and gaps of coverage in the Institute's investigator-initiated research; these projects are carried out through contracts to universities, research institutes, industry, and other organizations in the scientific community;

(iv) By supporting and stimulating training and instruction in the research and clinical aspects of cardiovascular and respiratory diseases;

(v) By organizing task forces and workshops to research and analyze key problems and to develop concrete proposals for actions that command the attention of the scientific and lay communities;

(vi) By promoting the coordination of all such research and activities and the useful application of their results; and

(vii) By collecting and disseminating information on these diseases.

This report highlights some of the major developments during FY 1972 in each of heart and blood vessel diseases, blood diseases, lung diseases, and technological development.

Diseases of the heart and blood vessels account for more than 54 percent of all deaths in the United States, and the economic drain of heart disease alone has been estimated at more than $30 billion. Among the major high-priority disease problems tackled by the Institute during FY 1972 were: arteriosclerosis; hypertension and kidney diseases; and other cardiac and cardiovascular diseases.

The Institute's Task Force on Arteriosclerosis submitted a two volume report to the Institute in final form in December, 1971. This report contained detailed recommendations for programs to be implemented in the near future as a result of new research findings. Specific recommendations included a national, coordinated, comprehensive program for the prevention and control of arteriosclerosis; the development of new national resources such as centers for prevention, cardiovascular disease prevention clinics, and an office of health education within the Institute; clinical trials to test the "risk factor" hypothesis that modification of risk factors such as smoking, hypertension, and food intake can help prevent arteriosclerosis; expansion of lipid research clinics; a clinical trial to test the effect of intervening on several risk factors in one and the same person; studies to reduce death and disability from acute events of arteriosclerosis such as heart attacks and strokes; recommendations for research manpower development and training; and managerial aspects of arteriosclerosis, such as the giving of incentives to the food and tobacco industries to make their products commensurate with optimal human health.

The Report by the Task Force on Arteriosclerosis is being used by the Institute in future program planning in this area. Further, new legislation introduced in Congress during FY 1972 utilizes several of the recommendations. This legislation, if passed, would enable the Institute to be more responsive to national needs in arteriosclerosis as well as other associated research areas. Finally, the President appointing a Panel on Heart Disease is in keeping with the recommendation by the Task Force that the federal role in the prevention and control of arteriosclerosis be expanded. The Chairman of the Panel is Dr. John S. Millis, President and Director of the National Fund for Medical Education. The Panel held its first meeting on May 18 - 22, 1972, and will be reporting to the President on September 1, 1972. The charge to this panel is: (1) To describe the problem of heart and blood vessel diseases as they present a threat to the individual, to certain groups of individuals, and to the nation. The panel is to highlight significant statistics on the magnitude of the morbidity, disability, and mortality problem, especially for diseases that have a large impact or those which are amenable to control; (2) To describe the current state of knowledge of these diseases and of measures for their control. The panel is to especially point out where medical technology is ready for application and where significant gaps in knowledge exist; and (3) To recommend highly feasible actions to implement the control measures identified and actions to secure information that will fill gaps in knowledge. These very specific recommendations are to be presented in a very broad context with respect to their impact on the individual, the nation's economy, and the nation's health manpower and

facilities. The panel is to estimate the extent to which each action can have a beneficial effect on morbidity, disability, and mortality, and the financial cost of each action, i.e., cost-benefit analysis.

Also as a follow-up of the Report by the Task Force on Arteriosclerosis, the National Heart and Lung Institute held a panel on Peripheral Vascular Disease on February 28 and 29, 1972. The Task Force had considered peripheral vascular disease as one of the major manifestations of the arteriosclerotic disease process. In the course of its studies of morbidity and premature death from arteriosclerosis the Task Force pointed out the striking disproportion between the current lack of medical progress in understanding, diagnosing or treating peripheral vascular disease and the prevalence of this disorder in the United States population. In addition, the political-social-economic implications of the disability and mortality of this disorder were explored. Finally, with respect to the process of arteriosclerosis itself, it was noted that easily detectable or overt peripheral vascular disease is frequently associated with occult life threatening complications of arteriosclerosis, such as myocardial infarction and stroke. In recognition of these conclusions of the Task Force, the Institute decided to further explore the needs in peripheral vascular disease by convening a special meeting. Certain topics were singled out for consideration. These included: mass screening of peripheral vascular disease with particular emphasis on the detection of the presymptomatic state; effective delivery of medical and surgical therapy by exploiting fully all available knowledge and techniques; development of newer and more effective measures and techniques for diagnosis and treatment; improving the teaching of peripheral vascular disease in medical schools and in allied health schools; and provision for continuing education of all concerned with peripheral vascular disease, ranging from patient to physician. The report by the panel is in preparation and will be submitted to the Institute during June, 1972.

A Workshop on Hormones and Arteriosclerosis was held on March 9, 10, and 11, 1972 to explore the relationship between hormones and arteriosclerosis. Endocrine factors have been implicated in the development of arteriosclerosis. However, our understanding of the specific role of these factors is at the "mixed" stage, i.e. there is a considerable amount of basic research information whose application to arteriosclerosis is speculation; and there is a far smaller body of work with really suggestive leads to the particular health problem of arteriosclerosis. The Workshop participants were requested to point out areas in which knowledge was inadequate and in which further research is needed. Finally, it was emphasized that questions of methodology should be considered both as to standardization of techniques and development of new techniques which could be applicable to these problems. It was noted that in a number of new Institute programs clinical populations are being assembled for study, and that these populations might be useful for studying certain of these interrelationships. The program was restricted to three areas: (1) steroid hormones; (2) peptide hormones; and (3) diabetes, and the participants were requested to develop recommendations for a national program to explore the relation-

ship between hormones and arteriosclerosis. The report by the workshop is in preparation and will be submitted to the Institute during June, 1972.

Once the clinical manifestations of arteriosclerosis are apparent, the consequences may be difficult, if not impossible, to correct. Since at least half of the patients who develop heart attacks die before receiving medical care, only primary prevention can effect a significant reduction in the number of sudden deaths. Three particular risk factors are amenable to modification and presumably to prevention of arteriosclerosis: hyperlipidemia, hypertension, and cigarette smoking. During FY 1971 and FY 1972 the Institute initiated a series of studies to test the hypothesis that modification of these risk factors would significantly alter the prognosis of patients with arteriosclerosis.

The test of the lipid hypothesis, i.e. that lowering of abnormal levels of blood lipids will result in reduction of the risk of heart attacks, is being carried out both at the Institute in Bethesda and in the Lipid Research Clinics described in last year's annual report. The Bethesda study is relatively small but intensive. It is being carried out on about 250 patients with Type II hyperlipoproteinemia, and the progress of the disease is followed by coronary angiography and exercise stress testing. A second clinical trial is in the planning stages. This trial will ultimately involve 3,600 people and will be an integral part of the six lipid research clinics established in 1971 and in the six more added in 1972. The plan is to carry out this study on subjects with Types IIa or IIb hyperlipoproteinemias, who are free of angina or myocardial infarction. Patients receiving a low cholesterol diet will be compared with a group receiving a lipid-lowering bile acid sequestrant in addition to the diet. The major endpoints for this five year study are sudden death and fatal or non-fatal myocardial infarction.

As mentioned in last year's annual report the Institute has initiated a program to develop and evaluate methods of detecting and caring for hypertensive persons in the population at large. The first phase of this study, now in progress, is concerned with determining adequate methods for detection and motivation of the approximately 10,500 persons from these selected areas, who are expected to have high blood pressure. It has been determined from Phase I studies that 14 - 15 clinical centers, each with approximately 800 participating subjects will be required for the study. The definitive phase of the planned trial would commence in 1973 if these centers could be funded in FY 1973.

During FY 1972 the Institute started the largest single clinical trial it has ever undertaken to test the effects of multiple risk factors - smoking, high blood pressure, and elevated lipids together - and their relationship to heart attacks, strokes, and other events. This program is called the Multiple Risk Factor Trial and is scheduled to last for ten years. It is a very important study since it is expected to give a definite answer to the question whether it is possible to interfere with the process of arteriosclerosis once it has started. This study will be

conducted in cooperation with a number of centers throughout the United States and will involve long-term, careful study of more than 10,000 people.

Important developments have occurred in the elucidation of the biochemical and physiological processes associated with ischemic myocardium. For instance, recent studies have demonstrated early subcellular changes in the mitochondria and transient myofibril changes. An analogue of angiotensin has been synthesized which appears to enhance energy production by ischemic cardiac tissue without simultaneously causing increased workload upon the heart due to elevation of blood pressure. The effects of glucose-potassium-insulin upon the size of experimental infarction and that of the enzyme hyaluronidase have also undergone favorable laboratory studies and are soon to be clinically implemented. Nitroglycerin has been found to have a beneficial effect in patients with acute myocardial infarction and left ventricular failure. Among metabolic indicators of prognosis, serum cortisol levels in excess of 20 micrograms per deciliter have been shown to have a high association with the subsequent development of left ventricular failure, arrhythmia, shock, or death, in contrast to lower values. In support of previous studies, elevations of free fatty acids (for example, above 1,100 micro-equivalents per liter) and elevation of urinary catecholamines (in excess of 12.5 micrograms per deciliter) show correlation with an adverse prognosis.

Important new information has been developed by the Centers for Specialized Research in Hypertension. No publications have yet appeared in the open literature, but two of the Centers have reported that they have been able to extract and purify renin from salivary glands. Attempts will now be made to clarify the structure of this compound. No one has been able to obtain a pure preparation when renin was extracted from kidneys. Studies in one of the Centers have shown that no cerebral accidents or coronary events were found in patients with essential hypertension and low plasma renin activity. If this finding stands the test of further scientific scrutiny, it could mean that plasma renin activity is an important factor in the development of atherosclerosis.

The NHLI is coordinating a new effort on sickle cell disease within the HEW. It is being assisted in this effort by a new HEW Sickle Cell Disease Advisory Committee, chaired by Mrs. Ruth Aikens, associate director for Health and Health Programs, National Urban League, New York. Sickle cell disease, the most common inherited disorder in the U.S. is believed to be present in more than two million black U.S. citizens. Although the disease occurs in a relatively benign "carrier" form in most of these people, approximately one in every 500 black infants is born with the life threatening form of the disease called sickle cell anemia. Several new approaches are in progress in sickle cell disease research. These include early diagnosis, the development of more accurate and economic ways of diagnosing the disease, and the use of pharmacological agents to prevent or alter the sickling process. Clinical trials aimed at altering the vaso-occlusive phenomena are in progress. These trials consist primarily of the use of urea, cyanate and carbamul

phosphate in an effort to alter deoxyhemoglobin S so that it will not crystallize and result in sickling of the red blood cells.

A broadened program in pulmonary research is one of the Institute's highest priorities. Lung diseases afflict the young and the old. In the newborn the most common cause of death is the dreaded respiratory distress syndrome which affects between 50,000 and 100,000 babies in the United States each year, about half of whom die. RDS is implicated in the development of adult respiratory disease as well. Of the adult respiratory diseases, emphysema and chronic bronchitis are the major killers. Emphysema, chronic bronchitis and asthma were the underlying cause of more than 30,000 deaths in 1970, and the contributing cause of twice that number. These diseases represent a particularly pressing health problem since the death rate and prevalence of these conditions has been increasing at an alarming rate over the past fifteen years. The number of deaths from emphysema and chronic bronchitis is currently doubling every five years. Emphysema alone is the fastest rising of any cause of death in the United States today. As a disabling disease, it is second only to heart disease.

As part of the Institute's long-range effort to sharpen the focus of its research planning in respiratory diseases so that it will be particularly responsive to national health needs, the Institute has solicited the counsel of a Task Force on Respiratory Diseases. This Task Force will report to the Institute by August 1972 on (1) national health problems associated with the various respiratory diseases, (2) the effectiveness of the current research effort addressed to each of these disease categories, and (3) the professional judgments of the members of the Task Force and their consultants as to research approaches warranting particular attention in the Institute's planning efforts. Complementary to the work of the Task Force, the Institute has analyzed its current research effort in terms of disease categories, and has also awarded a contract to (1) assess the current level of professional manpower in the pulmonary field and (2) estimate the pulmonary manpower requirements for academic medicine and national health care delivery. To aid the Institute in its overall planning, an expanded Pulmonary Diseases Advisory Committee has been constituted. Its fourteen members represent the different pulmonary disease categories and a range of interests from fundamental research to clinical medicine.

Specialized Centers for Research in Pulmonary Diseases were activated in eleven institutions throughout the country, and a second competition for additional Pulmonary Centers was held during FY 1972. The active Pulmonary Centers include two devoted solely to pediatric pulmonary diseases, four with major emphasis on the epidemiology of pulmonary diseases, and one with its focus on pulmonary care. To capitalize on the resources within its Pulmonary Centers and the regular research grant programs, the Institute has arranged a series of workshops addressed to specific problems. These workshops bring together investigators and a panel of experts who serve as consultants, leading discussion and formu-

lating recommendations for the guidance of the Institute in its future planning. A Workshop on Epidemiology of Respiratory Diseases was held in October, 1971, and a Workshop on Pediatric Pulmonary Diseases, in February, 1972. Reports of these workshops have been prepared for dissemination to interested investigators.

The Institute is supporting a number of programs which are intimately related to advances in technology, and which would not be possible without these aids. Some of the most prominent areas are: cardiovascular surgery and cardiac valves, pacemaker development, development of cardiovascular and respiratory life support devices, and new diagnostic procedures. Significant progress has been achieved on the engineering aspects of completely implanted heart assist devices and a totally implantable artificial heart. A completely implantable heart assist device driven by nuclear power has been developed and subjected to initial tests in animals. Clinical trials of a new capillary oxygenator are in progress.

Some of the new appointments within the Institute during FY 1972 were: Dr. Stella Booth, Chief, Respiratory Diseases Branch; Mrs. Juanita Cooke, Equal Employment Opportunity Coordinator; Dr. Clarence Dennis, Chief, Medical Devices Applications; and Dr. Rudolph E. Jackson, Chief, Sickle Cell Disease Branch.

PHS - NIH
NATIONAL HEART AND LUNG INSTITUTE
July 1, 1971 to June 30, 1972
OFFICE OF HEART AND LUNG INFORMATION

The primary goals of the Office of Heart and Lung Information are:

- to promote public understanding of the National Heart and Lung Institute and to enlist public support for its research and training activities directed against cardiovascular and lung diseases;

- to disseminate to the general public and to health professions the results of research carried out or supported by the Institute;

- to publicize and promote new programs in order to generate interest and encourage participation by members of both the general and scientific communities.

This report will summarize OHLI activities during Fiscal Year 1972 in the following areas: (1) information documentation and retrieval; (2) internal reporting; (3) public and professional inquiries; (4) press and media services; (5) publications; (6) exhibits; and (7) a separate accounting of OHLI information activities pertaining to sickle cell disease and the Institute's role as coordinating agency for the recently expanded federal Sickle Cell Disease Program.

INFORMATION DOCUMENTATION AND RETRIEVAL

Whatever the medium used for disseminating information -- pamphlet, report, press release, film, speech, exhibit, script, letter -- authentic and adequate subject matter is the required ingredient. Hence an activity basic to operation of the Office of Heart and Lung Information is the systematic development of information resources. This assures that essential stores of data and documents will be at hand from which to draw facts for the substantive content of informational products and services.

During the past fiscal year, source and reference materials acquired and maintained by the OHLI continued to be systematically developed. Documentation of research conducted and supported by the Institute involved the regular screening of more than 400 journals, with bibliographic recording of an estimated 3,500 NHLI-credited scientific papers during the year. Reprints of many of the papers were obtained and added to OHLI's reference materials in order to have them readily available for use by the staff in carrying out information functions and developing informational products.

Other categories of information resources also continued to be developed. Source files of selected materials pertaining to subjects of special or current interest were somewhat enlarged. The numbers of reference texts and index volumes were slightly increased. The collection of reports, memoranda, publications, and other materials relating to the background, programs, and

activities of the NHLI grew during the year. Frequently consulted, these resources provided access to subject matter needed for a wide range of informational purposes and proved valuable not only to the information staff but to other units of the Institute as well.

Two bibliographic reports regularly prepared were the "Monthly Listing of NHLI Staff Papers Submitted for Publication and/or Presentation," compiled for NHLI internal distribution, and "Quarterly Listing of Published Papers by NHLI Staff." Also compiled and edited for publication was material for the NHLI portion of the NIH Scientific Directory 1972 and Annual Bibliography 1971. Revised material was prepared for the NIH Almanac 1972.

PUBLIC AND PROFESSIONAL INQUIRIES

Responding to public inquiries is a major activity of the OHLI. Each day last year, OHLI received more than 200 letters and 25 telephone inquiries and personal visits from the general public, physicians and other professional health personnel. Although our response to public inquiries often consists entirely of a telephone conversation or letter, the provision of one or more publications is the mechanism whereby most inquiries are handled.

Although normally a function of the Clinical Center Special Events Section, the OHLI arranged and conducted, in whole or part, five tours of NHLI research facilities for visiting physician-scientists (Polish, French, Japanese, and Soviet, respectively) and a group of 50 exceptional students from Hahnemann Medical College.

PRESS AND MEDIA

Press and media services included arranging for three press conferences and three lectures; the preparation of 34 press releases, background statements and announcements; arranging approximately 75 interviews with members of the NHLI professional staff for representatives of the press, radio and television; and providing background information and other data (including 4,300 photographic prints and slides) in response to approximately 600 press and media inquiries.

INTERNAL REPORTING

Internal reports -- reports intended for use within NIH, HEW or other components of the federal government -- included three reports for use during Congressional appropriations hearings, two speeches, and more than 50 other reports such as outlines of major research topics, NIH Record articles, and weekly science and activity reports.

OHLI also responded to approximately 800 internal inquiries including 70 Congressional and Presidential inquiries; produced original art work for 50 charts and photographic slides; and edited at least seven technical manuscripts, reports and other presentations.

PUBLICATIONS

During this reporting period, the OHLI Publications Unit distributed 1,017,365 publications in response to 52,453 requests. Of this volume, 816,143 copies of the series "Dietary Management of Hyperlipoproteinemia" were distributed in response to 19,857 requests. This series, currently being revised under the direction of the NHLI Molecular Disease Branch, has been distributed in the amount of 2,075,000 copies since its first printing in February 1970.

The Publications Unit also handled the production and distribution of the NHLI Task Force on Arteriosclerosis, Volumes I and II. These volumes encompassing all areas of the problem of arteriosclerosis have been widely distributed to research institutions, medical libraries, associations, foundations, hospitals and medical schools. This Unit also assisted other NHLI components with the preparation and production of printed materials: NHLI Twin Study Brochure (CA), NHLI Fact Book (OD), Conference on Animals in Research (MDAB), and Fact Sheet: Blood Banking in the U.S. (NBRB).

The Publications Unit completed the production of the leaflet Type II Coronary Intervention Study. This leaflet, distributed to the medical societies of Washington, D.C., and six nearby counties in Maryland and Virginia, is aiding in recruitment of patients for this 5-year study by the NHLI's Cardiology and Molecular Disease Branches.

Publications reprinted this fiscal year include: Epidemiology of Stroke, Framingham Heart Study, Handbook of Heart Terms, A Living Pump, Hardening of the Arteries, and Sickle Cell Anemia (with permission of the National Institute of Arthritis and Metabolic Diseases).

This Unit processed for clearance, production and distribution, 34 press releases prepared by the OHLI and distributed to 92,887 addressees, and established two new mailing keys: HIC-22 Basic Press in D.C. and New York; HIC-23 Black Press in the United States. In addition, 13 other mailing keys were circularized and up-dated.

This Unit coordinated the Fiscal Year 1971 Annual Report for the Institute, and is currently doing the Fiscal Year 1972 report. A staff member of this Unit has been appointed as production liaison to the NHLI EEO Committee. To date, one issue of a newsletter for staff distribution has been prepared.

EXHIBITS

During Fiscal Year 1972, OHLI presented scientific exhibits at 14 meetings with a total attendance of about 279,000 professional people. In addition to the informational value of these exhibits, the distribution of NHLI publications in conjunction with the presentation of exhibits is a major route of disseminating information, accounting for more than one third of publications distributed by OHLI.

The OHLI has constructed two new exhibits for presentation to medical groups. One of these, entitled "Medical Devices Applications Program," is a 10-foot

exhibit depicting new materials and artificial heart devices that have been developed under contracts by the NHLI's Medical Devices Applications Program.

The second is a 10-foot exhibit featuring the OPTISAT LTD-1500, an electro-optical device for the immediate and continuous measurement of blood oxygen saturation. Developed in the NHLI's Laboratory of Technical Development, the OPTISAT was chosen by Industrial Research, Inc. as a winner in the 1971 "I.R. 100" new product competition. The exhibit appeared at the Museum of Science and Industry in Chicago from September 22 to October 17, 1971, with an estimated audience of 200,000.

"Hyperlipoproteinemia," a 20-foot exhibit describing the NHLI system for identifying and classifying blood-lipid abnormalities, won an Honorable Mention Award for scientific exhibits at the annual meeting of the Southern Medical Association in Miami, Florida, November 1-4.

The OHLI contributed $7500 this year toward the cost ($33,000 total) of constructing an HEW-sponsored World Health Exhibit commemorating World Health Day and featuring U.S. participation in international health activities of the World Health Organization.

SICKLE CELL DISEASE INFORMATION ACTIVITIES

Burgeoning information activities with respect to the expanded federal Sickle Cell Disease Program make a separate accounting of these activities desirable.

The OHLI handled 400 public and professional inquiries for information on this topic. These inquiries, together with internal and press inquiries received by OHLI and inquiries handled by the Sickle Cell Disease Branch, resulted in a combined distribution of 42,000 Sickle Cell Anemia leaflets, and slightly less than 1000 copies of Sickle Cell Anemia; A Review of the Literature. Public and professional information materials prepared by OHLI include a fact sheet on sickle cell disease, a list of references to recently published technical articles, a list of voluntary health organizations active in fund-raising, screening activities, and/or research in sickle cell disease, and preliminary drafts of two forthcoming publications on SCD -- one each for the general public and professional health personnel.

OHLI also handled 34 Congressional inquiries, 48 press inquiries, and 168 internal inquiries; prepared one speech, three press releases, and a report on a proposed SCD educational campaign; and arranged one press conference -- all pertaining to sickle cell disease and the newly expanded federal program.

The mailing key, Black Press in the United States (HIC-23) mentioned previously, was established this year as a direct result of the need to disseminate news of this important program as quickly as possible to the black citizenry of this country.

NATIONAL HEART AND LUNG INSTITUTE

OFFICE OF ASSOCIATE DIRECTOR FOR LUNG PROGRAMS

ANNUAL REPORT

July 1, 1971 through June 30, 1972

Responsibility for planning, coordinating and implementing all facets of the National Heart and Lung Institute's mandate relative to diseases of the lung resides in the Office of the Associate Director for Lung Programs. This responsibility transcends the mechanisms--grant, contract, award, or intramural research--by which the Program's goals are to be realized. Responsive to problems of national health, the Program fosters research and supports training of biomedical researchers with the ultimate goal of eliminating, or at least minimizing, the health problems and economic burdens accruing from diseases of the lung. Since October 1970, with the appointment of an Associate Director for Lung Programs, an orderly plan for realizing the Program's objectives has been developed; both temporary and permanent advisory groups have been constituted to provide guidance in developing and implementing these plans; and several new programs have been initiated to meet urgent research and training needs in specific areas.

The first part of this report describes the operational aspects of the Office of Lung Programs; i.e., how it plans, coordinates and implements its responsibilities. The second part highlights current research and training activities addressed to problems of diseases of the lung.

PLANNING

To have an informed basis for its long-range planning, the Office of Lung Programs initiated two complementary activities: (1) a staff analysis of the Institute's current pulmonary research programs (grants, contracts, and centers) in terms of disease categories and research approaches, and (2) the appointment of a Task Force which will report to the Institute by the end of the current fiscal year. Comprised of ten experts representing the main pulmonary disease categories as classified by the Institute for analyzing its research activities, the Task Force on Research in Respiratory Diseases is charged to (1) assess the importance of each disease as a national health problem, (2) assess the effectiveness of current research in relation to problems of etiology and pathogenesis, diagnosis, treatment and prevention, (3) identify new avenues for research, and (4) recommend priorities for the Institute's research effort. Because each Task Force member has consulted with a number of other experts in his area of responsibility, more than 100 biomedical scientists or physicians will have contributed to the report.

The Institute's analysis of its own pulmonary research programs has been completed. It is abundantly clear that the current research program is not a balanced effort. While it addresses the important public health problems of chronic obstructive pulmonary diseases and respiratory distress

syndromes, there has been a notable dearth of studies on interstitial diseases and on diseases of childhood that are implicated in development of chronic respiratory diseases in the adult. With the award of six new centers before the end of the fiscal year, this imbalance will be corrected to some degree. New centers are addressed to granulomatous disease of non-infectious origin, chronic interstitial pneumonia, hypersensitivity pneumonitis, and cellular and subcellular responses of the lung to injury. The current program is also clearly unbalanced with regard to research approaches, leaning heavily to pulmonary physiology without sufficient emphasis on fundamental approaches to etiology and pathogenesis of respiratory diseases. A more explicit assessment of the program's balance will be provided in the report of the Task Force. The Office of Lung Programs will then, in consultation with the Pulmonary Diseases Advisory Committee and the National Advisory Heart and Lung Council, establish appropriate priorities for its long-range plans.

In another approach to soliciting professional judgments from the biomedical community so as to strengthen and coordinate its current activities, the Lung Program held the first two of a projected series of workshops addressed to specific problems. The first workshop was addressed to the epidemiology of respiratory diseases; the second, to pediatric pulmonary diseases in relation to chronic pulmonary diseases in the adult. Expert consultants in relevant fields, and investigators whose work is supported by the Institute's goal-oriented grants (SCOR), research grants, or contracts, discussed current and planned protocols and made recommendations for strengthening the Institute's programs in these areas. (Reports on these workshops are available for general distribution.) Subsequent workshops will be addressed to environmental medicine with particular reference to exercise, hypobaria and hyperbaria, and to biochemical studies and non-respiratory functions of the lung.

The Office of Lung Programs is also obtaining information about professional manpower in the pulmonary field. Although it is known that a number of academic institutions have not found suitable candidates to fill funded pulmonary positions, reliable data on pulmonary manpower are not available. The Institute has contracted for a study to determine the number and types of physicians and scientists engaged in pulmonary clinical practice as well as in academic medicine. These data, which will be available by the end of the fiscal year, will be assessed in relation to professional judgments about pulmonary manpower requirements in the immediate and more distant future.

The Pulmonary Diseases Advisory Committee was expanded this year to include fourteen members, representing such disciplines as biochemistry, physiology, pathology and epidemiology, and representing pediatric as well as adult pulmonary diseases. This Committee identifies research and training opportunities; evaluates current and future program needs in the pulmonary area; and provides advice on aims, progress and productivity of goal-oriented programs of the Institute, especially Pulmonary Specialized Centers of Research, Pulmonary Academic Awards, and contracts. It will also advise the Institute about relative priorities for the pulmonary effort, drawing

on resources such as the report of the Task Force. This Committee has attended meetings of both Pulmonary SCOR grantees and Pulmonary Academic Awardees to learn first-hand what is being done in these programs.

COORDINATION

Although activities relative to lung diseases are supported through a variety of mechanisms administered by different operational offices of the National Heart and Lung Institute, these activities are coordinated by the Office of Lung Programs. When special initiatives are identified as important to the conquest or treatment of respiratory diseases, they are supported through the mechanism(s) most appropriate for their implementation. For example, the epidemiology of chronic obstructive pulmonary diseases is a special emphasis at several Pulmonary Specialized Centers of Research (SCOR) which are administered by the Pulmonary Disease Branch of the Office of Extramural Research and Training. But complementing the activities of the Centers are studies of alpha$_1$ antitrypsin deficiency in relation to chronic obstructive pulmonary diseases supported through contracts administered by the Respiratory Diseases Branch of the Office of Collaborative Research and Development. Some epidemiologic studies are also supported through the Epidemiology Branch of the Office of Clinical Applications.

When activities administered by several operational offices are addressed to similar disease problems or research approaches, the Office of Lung Programs sees to it that these efforts are complementary and not redundant. If some facets of a disease problem are not receiving sufficient attention, the Institute's targeted programs (SCOR grants, contracts) provide an appropriate way of soliciting proposals addressed to these facets. This year new SCOR proposals have been invited by the Pulmonary Disease Branch and new contracts by the Respiratory Diseases Branch to fill specific gaps.

Coordination is also achieved through staff visits, workshops and meetings. When the Office of Lung Programs arranged the workshop on epidemiology of respiratory diseases, participants included investigatiors supported by SCOR grants and by contracts. When it held the workshop on pediatric pulmonary diseases, it invited investigators supported by regular research grants as well as by SCOR grants. And when SCOR directors and investigators met for their first annual meeting, recipients of Pulmonary Academic Awards were also invited to attend. Moreover, the recommendations emerging from such meetings and workshops are included in reports that are distributed for the information of interested investigators, however supported.

Some recommendations generated at workshops and meetings have urged coordination of specific activities. For example, the workshop on epidemiology of respiratory diseases recommended that minimal uniform procedures be established for pulmonary assessments used in epidemiologic surveys. In this instance the Office of Lung Programs arranged for subcommittees to meet and reach agreement on such procedures. These are now incorporated in epidemiologic studies supported by SCOR grants and by contracts and are a required part of epidemiologic studies presently under review.

IMPLEMENTATION

It should be noted that the largest segment of the current pulmonary research program reflects the interests of the biomedical community, which has over the years applied for support through the customary investigator-initiated regular research grant and program project grant mechanisms. Within the past two years, the Institute has initiated a targeted research effort supported through either of two mechanisms: (1) the Respiratory Diseases Branch of the Office of Collaborative Research and Development, which supports contracts, or (2) the Pulmonary Specialized Centers of Research (SCOR) program, which provides grants for studies that are responsive to the Institute's program goals. These activities will represent a larger segment of the activities of the Lung Program by the end of this fiscal year. Pulmonary Specialized Centers of Research are now active at eleven institutions, and a second competition now completed will add six more centers. Contracts have been awarded to thirteen institutions. Another competition for contracts, addressed to four areas identified by the Institute in its request for proposals, will be completed by the end of this fiscal year.

A third initiative is addressed to the deficit of pulmonary professional manpower. The Pulmonary Academic Award program, designed to attract the medical student to the pulmonary field and to strengthen the pulmonary curriculum at the grantee institution, was initiated in the last fiscal year.

The Pulmonary Branch for Intramural Research has been hampered in realizing its plans because of limitations on space and personnel, limitations which should be less restrictive in the next fiscal year. At present, the Intramural activities include pulmonary function testing for patients at the NIH Clinical Center, a service available to all NIH Institutes; consultations for Clinical Center patients; cooperation in research programs initiated by other sections of the National Heart and Lung Institute; and an educational program of biweekly seminars by invited experts in various fields relevant to problems of lung diseases. Plans for an expanded Intramural research program have been completed and will be implemented during the next fiscal year as space becomes available.

RESEARCH ACTIVITIES

Following is an overview of research on pulmonary disease problems supported through various mechanisms: grant, contract, or center program.

ETIOLOGY

To realize the ultimate goal--prevention of lung diseases--etiologic factors must be understood. Epidemiologic surveys to determine incidence and prevalence of these diseases and their association with suspected risk factors is one approach. Another approach is to study the natural history of a disease by prospective longitudinal studies. Still another, is the experimental study that focuses on specific risk factors and how

their modification affects development and course of the disease. Both exogenous (environmental) and endogenous (hereditary and physiological) risk factors are being investigated by these several approaches.

Environmental factors--particularly air pollutants--are implicated as both causing and aggravating diseases of the airways (especially emphysema, chronic bronchitis, and some forms of asthma) and interstitial and diffuse pulmonary diseases. Through epidemiologic surveys and longitudinal investigations into their natural history, occupational diseases are under study in workers in cotton mills (byssinosis), in asbestos mines and other trades where such exposure is high (asbestosis), in dusty trades (pneumoconiosis), and in coal mines ("Black Lung" disease, or coal dust pneumoconiosis). Chronic obstructive pulmonary disease is also being followed in these populations as well as in other selected groups that range from childhood to old age and that include Blacks of low socioeconomic status, Whites, Indians, Mexican-Americans and workers in some industries.

As a consequence of the Workshop on Epidemiology held by the Institute in 1971, most of these studies now have a minimal common base that permits data to be compared or pooled. By agreement, all epidemiologic studies supported by Pulmonary SCOR grants or by contracts use certain pulmonary function tests, a uniform version of the British Medical Research Council questionnaire, and a uniform method of preparing specimens for pathologic assessment.

Because of strong evidence that cigarette smoking is an exogenous risk factor in chronic obstructive pulmonary disease, it is receiving particular emphasis by the Lung Program. Epidemiologic surveys supported by SCOR grants or by contracts include information on smoking habits. Moreover, the Institute has invited contract proposals addressed to detection of animal models for study of the pathologic correlates to the physiologic changes induced in these animals by cigarette smoke. (Other studies on smoking are mentioned in the section on Pathogenesis, below.)

Recommendations from the workshop alluded to above have also been the stimulus to a request for contract proposals to identify populations characterized by particular occupational exposures, with the idea that these populations might later be accessible for prospective studies.

Hereditary factors are less well understood, but a valuable clue being actively pursued is the observation that individuals who are homozygous for deficiency of the enzyme inhibitor alpha$_1$ antitrypsin seem predisposed to develop an emphysema-like disease. Still to be learned is whether individuals who are heterozygous for this deficiency are also at greater risk. Population surveys and studies of family aggregations are supported by Pulmonary SCOR grants, research grants, contracts, and through the Institute's Clinical Applications Program. Populations being studied for alpha$_1$ antitrypsin deficiency include Blacks of low socioeconomic status, Indians, Mexican Americans, and Whites in some industrial groups. The Clinical Applications Program is studying groups in Yugoslavia, Honolulu and Puerto Rico.

To insure uniform procedures, investigators supported by SCOR grants or by contracts have agreed to similar techniques for obtaining samples and assaying them. Moreover, two reference laboratories for alpha$_1$ antitrypsin determinations are supported by contract.

It is well known that not all persons exposed to exogenous risk factors develop chronic lung disease. The Workshop on Epidemiology recommended that host factors (endogenous factors) be studied to learn why persons with similar environmental exposures do not necessarily respond similarly. Stimulated by this recommendation, the Institute invited contract proposals for investigations of host factors, including immunologic, endocrinologic, genetic factors, etc., that might be implicated in chronic respiratory diseases.

The etiology of respiratory distress syndrome (hyaline membrane disease), a pediatric disease that is a major cause of infant death, is being investigated by several groups. Primarily a disease of prematurity, suspected risk factors are stresses during pregnancy or at parturition that compromise the neonate's circulation, affect control of ventilation, affect development of alveoli, and that modify production of the surface active material (surfactant) which is necessary to maintain the integrity of alveoli. Neonates as well as fetal lambs are being investigated to determine serum enzyme and surfactant levels associated with respiratory distress syndrome. And the effects of hypoxia, acidosis, and pulmonary ischemia are being studied in animal models.

PATHOGENESIS

To elucidate the changes at molecular and cellular levels by which diseases develop and by which their course is modified, investigators are drawing more and more upon the fundamental disciplines of biochemistry and biophysics, immunology, cell biology, pharmacology, etc. The Pulmonary SCOR grant and the more traditional program project grant are particularly suitable supportive mechanisms for facilitating interaction among basic and clinical scientists whose common goal is the solution of problems of human disease. Through these interdisciplinary grants, as well as through regular research grants and contracts, the Institute supports a spectrum of investigations that includes the natural history of respiratory diseases in man and the factors that affect their course; and, in both man and animal models, the underlying molecular changes and tissue responses to exogenous as well as endogenous insult.

Complementary to human case history (prospective) studies of chronic obstructive pulmonary disease are animal studies addressed to biochemical and cellular changes in the respiratory system that result from exposure to noxious gases, chemical aerosols, tobacco smoke, and other environmental pollutants. The roles of macrophages and ciliated epithelium as clearance mechanisms, and of immunologic responses to infectious agents and other antigens as defense mechanisms, are under study. Related to the possible role of proteolytic enzymes in development of emphysema (as in alpha$_1$ antitrypsin deficiency), emphysema-like lesions are being studied in animals exposed to papain--a proteolytic enzyme. To encourage more

work on specific aspects of the problem of cigarette smoking, the Institute invited contract proposals for the development of animal models to study the effects of various biologically safer cigarettes that are being developed elsewhere.

Hypersensitivity reactions, which are implicated in the development of both infectious and non-infectious respiratory diseases, are beginning to receive more attention and will have greater emphasis in the Institute's Lung Program in the future. Possibly a hypersensitivity disease, sarcoidosis is presently under study. This non-infectious granulomatous disease is ten to seventeen times as prevalent among Blacks in this country as among Caucasians. Several grants support studies addressed to its diagnosis, pathogenesis and natural history.

Center grants to be awarded before the end of the fiscal year virtually all include use of the techniques of immunobiology, identify possible antigens, and correlate immunologic information with morphologic changes in animal models.

To gain insight into the pathogenesis of respiratory distress syndrome (RDS) of the newborn, investigators are developing techniques for identifying the specific cells that elaborate surfactant and for determining whether the fundamental defect in this syndrome is a failure to elaborate the surface active material, a failure to store it, or a failure to secrete it.

Cystic fibrosis, a pervasive disease which also affects the respiratory system, is being studied, beginning in childhood, to better understand its natural history.

PHYSIOPATHOLOGY

The physiologic alterations characteristic of pulmonary diseases, or consequent to them, have long been a major emphasis in the regular research and program project grants. These studies are now complemented by targeted research supported through SCOR grants or contracts.

Research projects on lung function include physiologic studies of mechanics of breathing, ventilation-perfusion balance, and on chemical, nervous and humoral factors in control of ventilation. Similar studies are also part of some SCOR programs. But investigations of lung function by SCOR grantees are turning increasingly to the development of tests that will identify disease before it becomes both symptomatic and irreversible. Present diagnostic assessments are suitable for determining the severity of chronic obstructive pulmonary disease, but there is a pressing need for techniques that will identify changes at the time of the earliest lesions.

Hemodynamic studies are important to an understanding of pulmonary vascular diseases, but also have implications for respiratory distress syndrome. Investigators are studying blood volume and pulmonary capillary flow

in the newborn to determine hemodynamic changes associated with respiratory distress syndrome in the neonate. Hemodynamic factors involved in fluid transudation are also being studied for clues to their role in development of the pulmonary edema associated with respiratory distress syndrome.

Lung pathology and particularly the study of ultrastructural changes are part of most investigations, whether addressed to etiology, pathogenesis, or physiopathology of a disease.

Changes in connective tissue of the lung are receiving increasing attention in the context of emphysema, which is characterized by a structural failure of collagen fibers; of pulmonary fibrosis, which is characterized by collagen proliferation; and in respiratory distress syndrome of the newborn, where it may provide a clue to the stage of prematurity.

THERAPY

Because the course of many respiratory diseases is irreversible by the time symptoms are manifest, research on therapeutic intervention is largely addressed to alleviation of chronic pulmonary disease symptomatology, and to supportive measures to carry patients through episodes of acute respiratory distress. As part of its long-range plans, the Institute awarded contracts for a systems study to assess the problems of diagnosing, treating and monitoring patients with respiratory diseases, and also to assess the adequacy of support systems presently in use. These assessments will provide a guide for development of particular devices.

In the Institute's current program, membrane oxygenators are being developed and evaluated under contracts administered by the Medical Devices Applications Branch, and the Kolobow membrane lung is being developed intramurally.

Investigations directed to therapy for chronic obstructive pulmonary disease are addressed primarily to exercise regimens. However, quite recently interest has been extended to the role of psychological approaches to rehabilitative therapy. Both types of studies are supported through Pulmonary SCOR grants. In this context it is worth noting that well designed, well controlled assessments of the efficacy of such rehabilitative efforts are needed.

Ventilatory assistance is receiving particular emphasis with regard to treatment of respiratory distress syndrome of the newborn. The use of continuous positive airway pressure is under study at several centers supported by Pulmonary SCOR grants.

Some fundamental studies are also related to modes of therapy. The oxygen-rich mixtures used in therapy are known to cause lung damage on prolonged exposure. To achieve the benefits of oxygen therapy, without the untoward effects of oxygen toxicity, depends on an understanding of the mechanisms by which oxygen induces lung damage. While some research grants are addressing this problem, to encourage more research in this

important area the Institute has also awarded a number of contracts. Some of these are addressed to changes at the sub-cellular level and to alterations in biochemical pathways. Others are studying modifications in mucus clearance, first in animals, then in humans exposed to high concentrations of oxygen. Because surfactant production also seems to be affected by oxygen concentrations of ambient air, some contracts include investigations of surfactant and lipid metabolism, investigations that are of particular interest in relation to respiratory distress syndrome.

In another approach to the problems of oxygen toxicity and oxygen therapy, the Institute supports program project grants that provide facilities to study the effects of hyperbaric oxygenation.

TRAINING ACTIVITIES

To extend the manpower base in pulmonary research and medicine, the Institute supports Graduate Training Grants which may have a primary focus on either clinical research or fundamental research training. These are proposals initiated by training program directors and reviewed by the Pulmonary Training Committee for scientific merit. Hence the training program's emphasis--as represented by active grants--reflects training interests of the research and medical community. It does not reflect either a preconceived geographic distribution in terms of local manpower needs or an orderly plan to meet national goals for training in specific facets of pulmonary research.

With few exceptions, pulmonary physiology--both fundamental and applied to clinical problems--is the focus of active training grants. Exceptions are two clinical pediatric programs emphasizing cystic fibrosis (one of these also includes infectious diseases); three providing fundamental research training with particular reference to environmental factors; one emphasizing pharmacology; one, pathology; and one clinical training program that includes training in epidemiologic research techniques.

It is noteworthy--especially in view of the importance of other fundamental disciplines, such as biochemistry, pharmacology, genetics, immunology, etc., to an understanding of the pathogenesis of pulmonary diseases--that even programs addressed to training in fundamental research scarcely mention these disciplines. Six grants allude to biochemistry, but as only a minor part of the program, and only two mention immunology, also as a minor part. Moreover, physiology is emphasized overall in terms of pulmonary function testing. The clinical emphasis of the pulmonary training programs is overriding: 80% (35 grants) provide clinical training; half of these are entirely clinical in focus, the other half also include training in fundamental research. Among the nine grants providing training solely in fundamental research, four emphasize basic physiology as it relates to respiratory or circulatory function; the other five emphasize environmental factors, pharmacology or pathology.

Through the Research Career Development Award (RCDA), the Institute provides salary support for young investigators whose research careers hold high promise. Of 21 RCDA recipients whose interests are in pulmonary problems, most are in departments of medicine (9) or physiology (5).

Other departments represented are anesthesiology (3), pediatrics (2), pathology, and biochemistry. Research emphases include mechanisms of ventilatory control (6), surface active lipids of the lung (4), pulmonary circulation in relation to gas exchange (3), alveolar structure in relation to function (2). Other areas of investigation are oxygen toxicity under hyperbaric conditions; oxygen transport at high altitude; airway responses to bronchodilators; effects of anesthetics on lung water; abnormalities of pulmonary capillaries in lung diseases; and a fundamental study of effects of decompression on gas bubble formation.

The Research Career Award (RCA) program provides salary support for investigators who have established research careers of a high order. Although no new awards have been made since 1965, RCA recipients approved prior to that time continue to receive support if their research productivity is sustained. At present, seven RCA recipients working in the pulmonary field are from departments of medicine (2), anesthesiology (2), physiology, anatomy, and surgery. However, irrespective of their departments of origin, all are involved in physiologic research.

Postdoctoral and Special Fellowships provide support directly to the recipient—rather than through the sponsoring institution—for a period customarily of one or two years, to obtain specialized training relative to a particular type of problem. Of 27 fellows (18 special, 9 postdoctoral) whose research interests are in pulmonary problems, most are sponsored by departments of medicine (9), physiology (4), bioengineering (4), or biochemistry (4). Other sponsoring departments are pathology (2), surgery (2), pediatrics and radiology.

The background of these fellows is noteworthy in that six received their doctoral degrees in veterinary medicine. Nine hold advanced degrees in non-medical disciplines: bioengineering (4), chemistry (4) and biophysics.

To a remarkable degree, fundamental disciplines are being brought to bear on a variety of biomedical problems. Three fellows are applying bioengineering principles to the study of respiratory control mechanisms, one is developing a mathematical model of capillary exchange, another is developing computerized monitoring systems for intensive care of infants with RDS. Three fellows are investigating the biochemistry of surface active lipids; two, the biochemistry of mucoproteins. Others are studying the biochemistry of mammalian lung exposed to environmental pollutants, the biochemistry of pleural fluid, pulmonary responses to antigenic stimulation, the histochemistry and electron microscopy of emphysematous lungs, and histamine release from mast cells by radioactive techniques.

Using more traditional approaches, fellows are studying pulmonary function (3), respiratory control under varying conditions (3), pulmonary lymph flow, pulmonary blood flow, pulmonary embolism, pulmonary edema, effects of drugs on lung function, and an electron morphometric analysis of diseased lungs.

The Pulmonary Academic Award program, initiated in 1970, was developed to strengthen pulmonary curricula in medical schools so that bright young physicians would find pulmonary medicine or pulmonary research an attractive career goal. To achieve this, the Award provides a salary for a pulmonary physician or researcher below age 40 who will devote his major effort for at least five years to improving the teaching of pulmonary disease problems to medical students. It also enables the recipient to broaden his personal horizon through visits to or training at institutions with strong pulmonary programs and through meetings with Institute staff and special consultants. Moreover, recipients are encouraged to maintain their interest in research to the extent possible within the limitations of the award. They have been invited to the general meeting of SCOR directors, where research programs were discussed, and will be encouraged to attend workshops and other meetings that are relevant to their interests. At present, all awardees are members of departments of medicine, but this is not a requirement of the program.

A special feature of the program is that preference is being given initially to schools where pulmonary programs need strengthening, provided they present an acceptable candidate. However, it is envisaged that the program will ultimately expand to include all eligible schools with an acceptable candidate. Although experience is limited because only four awards were made the first year and 12 more this fiscal year, the Institute and its advisory groups view this program as both viable and promising.

Viewing collectively the awards and fellowships discussed above, two-thirds are in clinical departments, chiefly medicine. But among fellows, half are in non-clinical departments, reflecting the purposes of the fellowship program; namely, to obtain specialized training over a limited period.

ANNUAL REPORT
of the
MEDICAL DEVICES APPLICATIONS BRANCH

July 1, 1971 through June 30, 1972

BRANCH SUMMARY

The Medical Devices Applications Branch (MDAB) has as its goal the reduction of deaths and disability from circulatory and respiratory diseases through the development of materials, instrumentation, and devices for prevention, diagnosis, monitoring, and treatment of such diseases. Implementation is through a contract-funded and goal-oriented program covering the following areas: 1) research and development of materials which are compatible with blood and other tissues; 2) the development of a family of circulatory devices and supporting technology designed to assist the failing heart or to replace the irreversibly damaged heart; 3) the development of devices and supporting technology for monitoring and treating patients with pulmonary diseases; 4) the development of new biomedical instrumentation for improved monitoring of patients and earlier and more effective diagnosis of diseases; 5) the preclinical and clinical testing and evaluation of medical devices; and 6) performance of special analytical and experimental studies to support overall program objectives in medical devices.

In March, 1972, Dr. Clarence Dennis left his Chairmanship of the Department of Surgery at the State University of New York to become Chief of the Medical Devices Applications Branch. The Branch had been under the direction of Dr. Lowell T. Harmison, Acting Chief since the death of Dr. Frank W. Hastings in March, 1971. During this period, a change was made in program philosophy and direction to permit medical devices developed under the MDAB to be brought to clinical study more rapidly and directly by the developers of those devices, on the basis of pre-clinical data obtained from third-party test and evaluation organizations. These changes were necessary to achieve a sensitive balance between patient benefit and risk while preserving an atmosphere of creativity for research and development on medical devices. Another change decreased the number of reports being generated by contractors while preserving adequate communications between contractors and the Institute.

In January of 1972, the first MDAB-developed device, the Dow capillary membrane oxygenator, reached the stage of limited clinical trial. After going through engineering and animal testing at the Illinois Institute of Technology Research Institute (IITRI) Test and Evaluation Facility, the oxygenator was used successfully in open heart surgery at Presbyterian-St. Luke's Hospital in Chicago and at Latter Day Saints Hospital in Salt Lake City, Utah. Data from this preliminary testing will be evaluated, and determination will be made of the availability of it for wider clinical use.

The MDAB sponsored a three-day Conference on Research Animals in Medicine, held in Washington, D.C., in January, 1972, which was attended by almost a thousand persons. The Proceedings of this conference are scheduled to be published early in the next fiscal year.

A major accomplishment of the Medical Devices Applications Program (MDAP) during the past year was the successful testing in animals, in February, 1972, of the first totally implantable and nuclear-powered artificial heart assist system. This accomplishment established the feasibility of such devices and indicates the potential for rehabilitation of certain kinds of cardiac disease patients by devices under development. Further development and testing are expected to produce data for evaluating the general therapeutic role of the artificial heart in relation to other forms of treatment in any specific case.

During the next fiscal year it is expected that the Program will continue the development of cardiovascular and respiratory life support devices. Three Requests for Proposals were issued in the areas of materials, assist and replacement heart devices, and instrumentation for development and utilization of medical devices and for patient diagnosis and monitoring. After review of responses from these RFPs, it is expected that a number of contracts will be awarded in these areas. Decisions on other areas in which the MDAP will support research and development will be made as early in fiscal 1973 as program needs and budget resources are identified and matched. Active efforts are being made to recruit a number of mature, well-known investigators to the staff.

RESEARCH AND DEVELOPMENT CONTRACTS OF THE MEDICAL DEVICES APPLICATIONS BRANCH

(Active during FY 1972)

ARTIFICIAL HEART . . . . . MD- 7

Aerojet General Corporation (NIH-71-2488). . . . . MD- 8
Azusa, California
Air Products and Chemicals, Inc. (NIH-69-2156) . . . . . MD- 9
Allentown, Pennsylvania
Albany Medical College (NIH-69-2050) . . . . . MD- 9
Albany, New York
Anatole J. Sipin Co. (NIH-71-2051) MD-10
New York, New York
Arco Nuclear Co. (NIH-72-2900) MD-10
Leechburg, Pennsylvania
Arkon Scientific Laboratories (NIH-70-2045). MD-11
Berkeley, California
Battelle Northwest (PH43-66-1130). MD-11
Richland, Washington
Cleveland Clinic Foundation (NIH-69-2184). MD-12
Cleveland, Ohio
Hamilton Standard Division (NIH-71-2069) MD-13
Windsor Locks, Connecticut
Montefiore Hospital (NIH-72-2902). MD-13
Bronx, New York
McDonnell Douglas Corporation (PH43-67-1408) MD-14
Richland, Washington
Physics International (NIH-69-2253). MD-15
San Leandro, California
Stanford Research Institute (PH43-67-1422) MD-15
Menlo Park, California
Statham Instruments, Inc. (PH43-68-1502) MD-16
Oxnard, California
Tecna Corporation (NIH-71-2035). MD-16
Berkeley, California
Thermo Electron Corporation (NIH-71-2065). MD-17
Waltham, Massachusetts
Thermo Electron Corporation (PH43-67-1116) MD-17
Waltham, Massachusetts
Thermo Electron Corporation (PH43-68-1455) MD-18
Waltham, Massachusetts
Thermo Electron Corporation (NIH-69-2182). MD-19
Waltham, Massachusetts
Thermo Electron Corporation (PH43-66-982). MD-19
Waltham, Massachusetts
Tyco Laboratories (NIH-69-32). MD-20
Waltham, Massachusetts
University of Minnesota (PH43-67-1122) MD-20
Minneapolis, Minnesota
University of Mississippi Med. Ctr. (PH43-67-1118) MD-21
Jackson, Mississippi

University of Mississippi Med. Ctr. (NIH-69-2185). MD-21
Jackson, Mississippi
University of Utah (NIH-69-2181) MD-22
Salt Lake City, Utah
Westinghouse Electric Corporation (PH43-67-1139) MD-22
Pittsburgh, Pennsylvania
Yale University (NIH-72-2901). MD-23
New Haven, Connecticut

ARTIFICIAL LUNG MD-24

Amicon Corporation (NIH-71-2367) MD-24
Lexington, Massachusetts
Brown University (NIH-69-2047) MD-25
Providence, Rhode Island
Dow Chemical Company (PH43-68-1387). MD-25
Walnut Creek, California
Dow Chemical Company (NIH-71-2360) MD-26
Walnut Creek, California
Dow Chemical Company (NIH-71-2368) MD-27
Walnut Creek, California
Esso Research & Engineering Co. (NIH-71-2369). MD-27
Linden, New Jersey
General Electric Company (NIH-71-2361) MD-28
Schenectady, New York
Geomet, Inc. (NIH-71-2432) MD-28
Rockville, Maryland
International Business Machines Corp. (NIH-71-2431). MD-29
Gaithersburg, Maryland
Medi-Physics, Inc. (NIH-71-2363) MD-30
Emeryville, California
North Star Research & Development Inst. (NIH-71-2364). MD-30
Minneapolis, Minnesota
Tecna Corporation (NIH-71-2430). MD-31
Berkeley, California
Union Carbide Corporation (NIH-71-2365). MD-32
Bound Brook, New Jersey
Washington University (NIH-71-2366). MD-33
St. Louis, Missouri

BIO-INSTRUMENTATION MD-34

Franklin Institute (NIH-69-2237) MD-34
Philadelphia, Pennsylvania
General Electric Company (NIH-69-2238) MD-35
Schenectady, New York
Geomet, Inc. (NIH-71-2429) MD-36
Rockville, Maryland
International Technical Industries (NIH-69-2240) MD-36
Santa Cruz, California

Konigsberg Instruments (NIH-69-2241). MD-36
Pasadena, California
Werner P. Schulz (NIH-71-2043). MD-37
San Bruno, California
Westinghouse Electric Corporation (PH43-68-661) MD-37
Pittsburgh, Pennsylvania

BIO-MATERIALS MD-39

Abcor, Inc. (NIH-71-2047) MD-40
Cambridge, Massachusetts
Battelle Memorial Institute (PH43-68-649) MD-40
Columbus, Ohio
Battelle Memorial Institute (NIH-71-2058) MD-41
Columbus, Ohio
Carnegie-Mellon University (PH43-66-977). MD-41
Pittsburgh, Pennsylvania
Dow Corning Corporation (PH43-66-979) MD-42
Midland, Michigan
Franklin Institute Research Labs., (NIH-71-2017). MD-42
Philadelphia, Pennsylvania
Gulf Energy & Environmental Systems, Inc. (PH43-67-1411). MD-43
San Diego, California
Johns Hopkins University (PH43-68-84) MD-43
Baltimore, Maryland
Lee Pharmaceuticals, Inc. (PH43-68-1379). MD-44
South El Monte, California
Lee Pharmaceuticals, Inc. (PH43-68-1409). MD-44
South El Monte, California
Polysciences, Inc. (PH43-66-1124) MD-45
Warrington, Pennsylvania
Providence Hospital (NIH-71-2060) MD-45
Seattle, Washington
Stanford Research Institute (PH43-64-84). MD-46
Menlo Park, California
State University of New York (PH43-68-75) MD-46
Brooklyn, New York
Thermo Electron Corporation (PH43-66-1126). MD-47
Waltham, Massachusetts
Union Carbide Corporation (PH43-68-1388). MD-47
Bound Brook, New Jersey
Union Carbide Corporation (NIH-71-2067) MD-48
Bound Brook, New Jersey
University of Michigan (NIH-71-2054). MD-49
Ann Arbor, Michigan
University of Vermont (PH43-68-1427). MD-50
Burlington, Vermont

MEDICAL DEVICE APPLICATION MD-52

Baylor College of Medicine (PH43-67-1424) MD-52
Houston, Texas
IIT Research Institute (NIH-69-2125). MD-52
Chicago, Illinois
Meloy Laboratories, Inc. (PH43-67-1418) MD-53
Springfield, Virginia
Travenol Laboratories (PH43-67-1425). MD-54
Morton Grove, Illinois
University of Utah (NIH-70-2081). MD-54
Salt Lake City, Utah

SPECIAL PROGRAMS - Artificial Heart Development MD-55

ARTIFICIAL HEART

A major goal of the Medical Devices Applications Program is the development of a family of devices which can be effectively used in the rehabilitation of patients with advanced heart disease. There exist clinical needs for devices which can 1) Temporarily assist the acutely failing circulation during critical periods of diagnosis and corrective treatment (emergency assist devices); 2) Assist the circulation for periods of days to several months in anticipation of eventual recovery of circulatory function (temporary assist devices); 3) Permanently assist the heart in cases of irreversible failure (permanently implantable assist devices); and 4) Totally and permanently assume entire function of hearts and end-stage failure (total heart replacement devices).

Development of devices to meet each of these four needs has progressed under MDAP contracts during FY 1972. Westinghouse, Tecna, and Hamilton Standard/Yale have developed intra-aortic balloon pumping devices, mechanical ventricular assistance cups, and external sequenced pulsation systems which can serve as emergency assist devices. Thermo Electron Corporation's left ventricular assist pump and bilateral assist system are designed to be temporary assist devices. The H-TAH pusher-plate version of the TECO left ventricular assist device is designed to be driven by implantable energy systems and as such represents a potential permanent assist device. Developments in total heart replacement are being made at the Cleveland Clinic, the University of Mississippi, and the University of Utah.

The potential merits of implanted power for driving circulatory assist and/or total heart replacement devices are significant. The major advantages of implanted power include patient mobility, freedom from external electrical sources, and the elimination of potential sites for infection. MDAP is proceeding along two specific approaches for achieving completely implanted power systems to permit patient rehabilitation. These approaches include: 1) the use of thermal energy derived from an implantable nuclear heat source (radioisotope), and 2) the utilization of energy from within the body as both the fuel and the oxidizer. The overall objective of the nuclear programs is to develop and test completely implanted nuclear powered cardiac assist systems that will assume the cardiac output of the left ventricle and operate in a synchronous counterpulsation manner. Each of the systems is being developed to operate with radioisotope-produced heat or by electrical energy which is transmitted across intact skin and stored in a thermal storage unit for subsequent operation of the internal blood pump system. No external connections are required. Details of the development of the targeted efforts of the Program in this area are presented in the Special Programs section.

During the past year, research and development in the energy area has been carried forward under five contracts. Three of the contractors are developing modified Stirling engines and one is developing a Rankine-cycle engine. The fifth contractor is developing a direct-acting engine blood pump system utilizing a combined Rankine-Stirling thermodynamic cycle. Prototypes of each system have been fabricated and tested. Some of the devices under development will soon be ready for initial clinical testing; the human appli-

cation of others lies farther in the future. All systems, however, are being intensively evaluated in both engineering and animal laboratories, and significant progress is being made.

AEROJET GENERAL CORPORATION, Azusa, California
Contract Amount: $402,220 Contract Number: NIH-71-2488 (formerly PH43-68-1435)

DEVELOPMENT OF A MODIFIED STIRLING CYCLE HEART ENGINE
(Mark Rudnicki, p.i.)

The goal of this effort is to develop an implantable, long-life, energy conversion system for heart assist and replacement devices. Specifically, the goal is successful development of a modified Stirling cycle energy conversion system utilizing either radioisotope energy storage or electrically recharged thermal storage. Steady progress has been made and results to date indicate excellent prospects for attainment of the goal. A power system has been developed which can convert radioisotope energy to useful pneumatic flow work for driving implantable circulatory assist devices. Five prototype engines have been developed. Mark I and Mark II were engineering prototypes which were developed to characterize engine performance. Mark III was developed and integrated with a ventricular assist device. In vivo tests demonstrated the basic feasibility of this system. Two advanced engines, Mark IV and Mark V, have also been developed. Mark IV is an instrumented prototype, while Mark V is an implantable system. The Mark V engine design can accept a 50-watt radioisotope heat source or periodic electrical recharges. Engine efficiencies of approximately 21% have been achieved with the Mark IV engine. Compactness and weight reduction advancements were achieved with these units by drastic bearing load reduction. Key engine component testing has been conducted on Mark V bearings, reverser, and check valves. A pump actuator and control (PAC) unit was developed through several iterations to a PAC-4 version. PAC-4 converts gas flow work to hydraulic oscillating flow work for driving and controlling a ventricular assist blood pump. PAC-3 was operated in vivo with a Mark III engine and a blood pump. The system successfully demonstrated reduction in ventricular systolic pressure. The PAC-4 together with the Mark V engine integrated with a radioisotope capsule has been tested in vivo with good results. Recent test results and planned design innovations indicate that the following milestones will be accomplished during the next twelve months program period:

- Reliable two year operating life;
- Continued in vivo system operation with radioisotope energy source;
- Twenty-seven percent overall engine thermal efficiency; and
- 1.15 liter system envelope volume including blood pump.

The proposed continuation program will include the completion of very thorough bench testing of the compact Mark IV and Mark V engines and PAC-4 actuator. This testing will be complemented by continued in vivo testing with ventricles and radioisotope energy sources. Design modifications will be developed to attain the objectives. New design concepts will be explored to advance the system capability beyond the stated objectives. Elimination of all engine wear surfaces will be explored.

AIR PRODUCTS AND CHEMICALS, INC., Allentown, Pennsylvania
Contract Amount: $10,000 Contract Number: NIH-69-2156
DEVELOPMENT PROGRAM FOR AN ENERGY CONVERSION SUBSYSTEM
(Clarence J. Hornbeck, p.i.)

The objectives of the Air Products program were to design, build, and test a modified Stirling converter and a pneumatic actuator-control subsystem to drive a blood pump. The system provides a very compact overall design which yields a high power density energy system. A breadboard engine has been developed and tested. This engine ran in a self-sustaining mode at speeds varying from 100 to 1975 rpm. At 350 rpm, the total heat input was 35.6 watts. Unlike the constant speed resonance type Stirling engines, this system contains a positive displacement actuator which has a no-stall characteristic. The combination of the positive drive and very light moving parts provides quick engine response. The system operated at normal design pressures of 1000-1200 psi, showing that high pressure engines with inherently smaller components can be fabricated. The compressor flow was lower than expected, and it appears that the development of compressor check valves must be emphasized. Actuator flow was about 20% of the ideal compressor output, but analysis indicates that this pneumatic loss may be cut by a factor of two. Due to funding limitations this program was phased out in an orderly manner and terminated October 5, 1971.

ALBANY MEDICAL COLLEGE, Albany, New York
Contract Amount: $46,802 Contract Number: NIH-69-2050
DEVELOPMENT OF MODELS OF CORONARY AND AORTIC ATHEROSCLEROSIS IN MINIPIGS FOR TESTING DEVICES
(K. T. Lee, p.i.)

The primary objective of this contract work is to develop, standardize and characterize animal models of advanced coronary and aortic atherosclerosis using Pitman-Moore miniature swine. The approach chosen was the feeding of a high-fat, high-cholesterol diet, administration of propylthiouracil and x-irradiation. A mild atherogenic diet consists of 8 gms of cholesterol as a daily additive to the mash diet normally given these animals. A severe atherogenic diet contains cholesterol, sodium cholate and propylthiouracil. Each of these diets, as well as the control mash diet, consisted of about 2500 calories. X-irradiation of 1500 r was given to the precordial region of the swine by using a Cobalt 60 source. Most swine received two x-irradiations at four-to seven-week intervals. Over the contract year 84 swine were included in the experiments. Of these, 22 swine fed the severely atherogenic diet died suddenly without apparent signs of sickness and were found dead in cages or pens; 90 percent had myocardial infarcts either healed, recent or both. In most of these swine the main coronary arteries were virtually occluded by atherosclerotic plaques; in the few in which the main coronaries were not occluded the secondary branches were severely occluded. It was concluded from these studies that both x-ray and high-fat, high-cholesterol diet are needed to produce a severe degree of atherosclerosis in a short time; diet alone will also produce these lesions but it takes a longer amount of time. In those swine that died suddenly, telemetry EKG was used to determine the mechanism of sudden death. This mechanism proved to be ventricular

fibrillation. The effect of removing propylthiouracil from the atherogenic diet was investigated. Preliminary results indicated that this latter diet is just as effective as the one which includes the propylthiouracil in producing ischemic heart disease and the complications of ischemic heart disease. The future direction of the research is to develop a model in which generalized atherosclerosis of significant degree can be produced in swine without the use of x-irradiation. It is envisioned that such a model may be useful to test instrumentation designed to detect early developing atherosclerosis.

ANATOLE J. SIPIN COMPANY, New York, New York
Contract Amount: $4,060 Contract Number: NIH-71-2051
MAGNETIC ENERGY CONVERSION SYSTEM
(Anatole J. Sipin, p.i.)
A study has been carried out with the objective of determining the feasibility of developing an implantable electromagnetic drive for powering an artificial heart. The major questions that required resolution were the efficiency that could be achieved with an electromagnetic pump of implantable size and the safety with which the conductive pumping liquid could be used. A search has been made of sources of information, including review of published material and inquiries of workers in the field. The applicability of various types of dc and ac electromagnetic pumps has been considered. Compatible materials for an efficient electromagnetic pumping system have been identified. Preliminary designs and performance analyses of multistage and single-pass dc conduction pumps have been made. An investigation has been made of rectifying devices for an implanted dc power supply. Control concepts have been generated for dc and ac pumping systems. Sodium-potassium (NaK) eutectic is considered to be the most suitable conductive liquid. Methods have been devised for the reliable containment of NaK. Development of a pumping liquid using a suspension of conductive particles is possible. Analysis of a system with a single-pass dc conduction pump and a solid state synchronous rectifier shows that, based on a calculated pump efficiency of 40%, an average pulsatile fluid power output of 8 watts can be delivered with a power dissipation of 25 watts. The conservative overall system efficiency, including the power supply, is approximately 25%. It is concluded that the development of an implantable energy conversion system utilizing an electromagnetic pump is feasible. This feasibility contract terminated December 21, 1971, at the end of the contract period.

ARCO NUCLEAR, Leechburg, Pennsylvania
Contract Amount: $423,701 Contract Number: NIH-72-2900
(formerly NUMEC: NIH-71-2053)
RADIOISOTOPE-POWERED ARTIFICIAL HEART
(M. Blair, p.i.)
The overall objective of this program is to develop a radioisotope-powered heart replacement system. The concept uses the thermal energy from a Pu-238 source to operate a Rankine-cycle steam engine at the physiological pulse rate. This effort was initiated late in 1970. The effort of the first phase has been directed toward component development and proof of feasibility using a bread-

board model. A second engine is being fabricated. If this proves the feasibility of this type of engine, future efforts will be devoted toward the engineering development of a series of sequentially refined models. Efforts will also be devoted to long-term reliability tests of materials and components.

ARKON SCIENTIFIC LABORATORIES, Berkeley, California
Contract Amount: $157,287 Contract Number: NIH-70-2045
DEVELOPMENT OF EFFICIENT, IMPLANTABLE SOLENOID ENERGY CONVERSION SYSTEMS FOR DRIVING ARTIFICIAL HEARTS
(Peer M. Portner, p.i.)
Development has continued on a solenoid driver system for actuating a blood pump, which delivers an output energy of 3.2 joules per stroke at a maximum solenoid efficiency exceeding 67% over a wide dynamic range of operation. A mechanical latching system has been developed, which replaces the previous magnetic clamping function in the solenoid actuation cycle and which provides significantly relaxed tolerances in design, fabrication and operating control as well as a means for automatic compensation for wear or other variation of parts during the life of the system. A feedback control system has been developed for automatic control of output energy which is responsive to rapid dynamic changes in pulse rate and aortic pressure (as observed experimentally) and to the volume of filling of the artificial blood pump. The system provides correction for incomplete pump filling from stroke to stroke and has built-in features to overcome stalling of the pump. An override pacemaker will not allow the pulse rate to drop below 40 pulses per minute. The system has been found to be completely responsive when operated over a wide range of variable load conditions in aortic pressure and inlet fill head in a mock loop in a single ventricle assist device mode. Typical overall system efficiencies exceed 30%. For peak systolic and end-diastolic pressures of 133/67 mmHg at 67 bpm, the cardiac output is 6.7 liters per minute for an equivalent hemodynamic power of 1.55 watts for an electrical input to the system of 5.2 watts. At increased rates the output exceeds 15 liters per minute at 150 beats per minute at a peak systolic pressure of 120 mmHg, dropping to about 10 liters per minute at 200 mmHg for an electrical input power of 11.5 watts. The compact solenoid drive system to be used in in vivo assist device experiments in calves at Stanford University School of Medicine weighs 3.9 pounds. Long range plans include completion of development and in vivo performance evaluation of totally implanted systems employing both one-and two-ventricle blood pump configurations.

BATTELLE MEMORIAL INSTITUTE, PACIFIC NORTHWEST LABORATORY, Richland, Washington
Contract Amount: $55,880 Contract Number: PH43-66-1130
A STUDY OF THE EFFECTS OF ADDITIONAL ENDOGENOUS HEAT RELATING TO THE ARTIFICIAL HEART
(M. Gillis, p.i.)
Total artificial heart implantation must include means for rejecting the added endogenous heat generated by the artificial heart power source-energy conversion system, preferably through physiologic channels of convection, conduction, radiation and evaporation. Electrically energized heaters were

designed conforming in size, shape and material to long-term implantation in the aortas of miniature swine. These were implanted and the animals maintained throughout the subsequent experimental period during which heater power and internal transducer feedout were provided via percutaneous leads. Results of prior contract years indicated that the miniature swine could tolerate power inputs up to and including 60 watts (4.7 watts per cm^2 flux) for extended periods without overt alteration of physiologic function or significant effects on hematologic and serologic parameters monitored. The following conclusions have been drawn from or further supported by the present contract year's research: (1) in the absence of high ambient temperature, concurrent systemic infection causing a fever, or occlusion of blood flow through the heat exchanger by thrombus formation at the junction of aorta and heater end piece, a female miniature swine will tolerate 60 watts added endogenous heat via a graphite-benzylalkonium-heparin coated heater in the thoracic descending aorta for 24 to 36 months without overt alteration of physiologic function. Specific heat input rates to the group of heated animals in this chronic study range from 0.6 to 0.9 watts per kilogram of body weight during the latter part of the experimental period and 1.1 watts per kilogram in the early months of heating. Flux at the heat transfer surface is 4.7 watts per square centimeter at 60 watts. (2) Hematologic and serum biochemical changes are minimal to absent in heated and control animals unless infectious or myeloproliferative disorders exist. (3) Renal lesions in long-term preparations are probably due to thromboembolism from developing thrombi at the junctions of aorta and heat exchanger; the kidneys of a 36-month, 60-watt preparation were grossly and histologically normal. (4) An extended area heater (graphite lumen, finned, with non-thrombogenic pyrolytic graphite coating by Gulf General Atomic) preparation attained 18 months of continuous heating at 60 watts with no clinical nor postmortem evidence of deleterious effect. Most significantly, there were no signs of downstream thromboembolic phenomena, further testifying to the excellent blood-compatible properties of this surface treatment. The work of this program has concluded and the contract will terminate on June 28, 1972.

CLEVELAND CLINIC, Cleveland, Ohio
Contract Amount: $60,400 Contract Number: NIH-69-2184
DESIGN AND EVALUATION OF A NATURAL RUBBER WAVE-PULSATING HEART
(Y. Nosé, p.i.)

A natural rubber wave-pulsating totally-implantable prosthetic heart was developed under contract. In the current contract year the design for the wave-pulsating heart was finalized, tooling to construct the heart was designed and fabricated, and a reliable reproducible hand-dipping fabrication technique was developed. In addition, a detailed mock loop analysis was performed to characterize hemodynamic properties of the prosthetic heart. The wave-pulsating heart has been demonstrated to be relatively thromboresistant and atraumatic to blood. Basic materials research performed at the Cleveland Clinic has generated a different type of total artificial heart device called the "biolized" heart. This device is constructed with biological tissue components such as aorta, aortic valves and pericardium. This aldehyde-treated natural tissue has shown excellent thromboresistant properties; in addition, because of the use of biological valves, the hemodynamic performance of the

prosthetic device is similar to that of the natural heart. Both the wave-pulsating and the biolized hearts are capable of cardiac outputs in excess of 10 l/min. A major thrust of the physiologic research over the past contract year has involved the characterization of the response of the lungs to artificial heart pumping. Two distinct patterns of pulmonary insufficiency have emerged, the first being a simple congestive atalectasis secondary to inadequate output by the left side of the heart, and the second being a pulmonary edema with normal venous pressures probably caused by direct damage to the pulmonary capillary bed during prosthetic heart pumping. The result is pulmonary insufficiency and has been the major cause of deterioration of test animals in which artificial hearts have been implanted. Further investigations will be directed toward further defining the mechanism of the pulmonary changes, to evaluate the comparative effects of the pulse pressure wave on the circulatory homeostasis, and toward achieving longer survival time so that a stable physiologic preparation is achieved.

HAMILTON STANDARD, Farmington, Connecticut
Contract Amount: $11,600 Contract Number: NIH-71-2069
SEQUENCED PULSATION IN THERAPY OF CARDIOGENIC SHOCK
(D. Porterfield, p.i.)
The "sequenced pulsation" device is a type of emergency non-invasive circulatory assist device; a compression suit is applied to the lower extremities by means of which external pressure is applied sequentially from the feet upward during cardiac diastole, producing a counterpulsation wave. Rapid release of pressure and application of vacuum during isometric systole increases vascular volume and thus reduces left ventricular afterload. A second generation device was designed and underwent preliminary testing in normal human volunteers at Yale, which showed that significant elevations in aortic mean diastolic pressure, and reductions in aortic end-diastolic pressure could be obtained. The contract terminated August 31, 1971; work is being continued under contract number NIH-72-2901 with Yale (See below.)

MONTEFIORE HOSPITAL AND MEDICAL CENTER, Bronx, New York
Contract Amount: $41,015 Contract Number: NIH-72-2902
(formerly LEESONA MOOS LABORATORIES Contract Number: PH43-68-1380)
STUDIES LEADING TO THE DEVELOPMENT OF IMPLANTABLE BIOLOGICAL FUEL CELLS TO POWER ARTIFICIAL HEART DEVICES
(J. H. Fishman & J. F. Henry, p.i.'s)
(Work on this contract was performed at the Leesona Moos Laboratories in Great Neck, New York, until December 1971. After an interruption of three months the program was reactivated with the same principal investigators at Montefiore Hospital and Medical Center, Bronx, New York.)

On the basis of earlier tests a fuel cell design concept was adopted in which the active electrodes are isolated from direct contact with the blood by blood-compatible porous membranes which permit permeation of the reactants to the electrodes. Parallel studies of electrodes, electrocatalysts, membranes, and cell design and operation were carried out. Electrodes were prepared by elec-

trodeposition of AuPd alloys from phosphoric acid buffered solutions at controlled potentials under various conditions of stirring, temperature, time activation, and other parameters and for different porous substrate sturctures such as fine metal screens and mats. Commercial membranes have been evaluated in terms of their filtering capacity for proteins and their diffusivity for oxygen, glucose, and other oxidizable compounds. There is an approximately linear decrease in potential of the anode (Au-rich AuPd alloys) when glucose concentration is increased from 1 to 2 grams/liter. A fuel cell has been designed and fabricated for use in in vivo experiments which will permit easy replacement and interchange of electrode structures. In vitro testing in aerated glucose-saline solutions and in ACD human blood has shown that under pulsed operation cells display greater stability and higher power outputs than under steady state operation. For example, at an open circuit potential of 550 mV the power output density was 200 microwatts/cm. It is expected that the next phase of work will include extensive in vivo performance evaluation of elementary low power level fuel cells in animals.

MCDONNELL DOUGLAS ASTRONAUTICS COMPANY, Richland, Washington

Contract Amount: $548,825 Contract Number: PH43-67-1408

DEVELOPMENT OF THE THERMOCOMPRESSOR AS THE POWER SOURCE FOR AN ARTIFICIAL HEART

(William R. Martini, p.i.)

The objectives of this effort are to design, fabricate and test radioisotope- and electric-heated implantable Stirling engines for circulatory assist devices. The heat engine under development employs a moving thermal regenerator oscillating in between a heated and a cooled end of a hollow cylinder. This regenerator serves to increase and decrease the average gas temperature almost reversibly, resulting in pressure and volume surges. Several different types of regenerators have been developed, including both porous and hollow-plug regenerators. The artificial heart engine under development has progressed logically through four distinct designs, each representing a significant improvement over the previous one. The operational feasibility of a total thermal system was demonstrated by in vitro and in vivo tests during the current contract year. One engine operated for over 5000 hours before a fly wheel bearing failed. This bearing was replaced and the engine tests continued. The key current accomplishments include: the reduction of thermal energy input from approximately 100 watts to 50 watts, an increase in engine efficiency from 5% to over 14%, an increase in overall system efficiency from approximately 2% to 6%, improved system thermal control, improved energy regeneration within the Stirling engine, the separation of working gas from the internal drive system of the Stirling converter, fabrication of a Pu-238 capsule, and in vitro and in vivo testing of a radioisotope-powered circulatory assist system. Major emphasis in the next contract year will be on improved operational performance, controllability of the engine, and longevity of operation. Several complete design and test iterations are planned to yield a system with an operational life of approximately two years. A re-evaluation of the regenerator drive system is being made in an attempt to replace the fly wheel drive with a linear free piston drive. Pump control, system heat rejection, power management, and component development activities will be continued.

PHYSICS INTERNATIONAL COMPANY, San Leandro, California
Contract Amount: $141,118 Contract Number: NIH-69-2253
DEVELOPMENT OF AN IMPLANTABLE PIEZOELECTRIC ENERGY CONVERSION SYSTEM FOR DRIVING AN ARTIFICIAL HEART
(C. G. O'Neill, p.i.)

Development has continued on a piezoelectric driver system with electronic pulser and control system for use in driving and controlling a blood pump. The system is based on the twin piezoelectric stack concept in which energy is transferred back and forth between two ceramic stacks which operate alternately as driver and storage capacitor at a piezoelectric pulse frequency of 50 hertz (cycles per second), thereby conserving energy and improving system efficiency. A hydraulic motion amplifier stage is used to transform the mechanical impedance of the system from the high force-low volume condition at the output of the stack to a low force-high volume condition at the input to the blood pump. The overall system operates at the natural cardiac rate and in bench tests in a mock loop has exhibited overall efficiencies exceeding 25% from electrical input to the system to hydraulic input to the blood pump. The engine uses epoxy-bonded piezoelectric stacks developed previously under this contract. Life testing on epoxy-bonded stacks has exceeded 10^9 cycles at high electric fields (excursion of 60 volts per mil) at 30 hertz operating frequency and are still running. Emphasis has been placed on solution of detailed electronic problems in switching and control circuits of the pulser and in mechanical design and performance problems associated with bellows reliability, control and check valve operation, and minimizing of compliance. Mock loop testing of the system in an assist device configuration with a simulated natural heart has demonstrated synchronous response to rapidly varying conditions of aortic pressure and pulse rate. Initial in vivo assist device experiments in calves are planned within the current contract period. Further optimization of this overall device and evaluation of performance in vivo will be conducted in the coming year.

STANFORD RESEARCH INSTITUTE, Menlo Park, California
Contract Amount: $246,422 Contract Number: PH43-67-1422
TRANSCUTANEOUS POWER TRANSMISSION SYSTEM
(Peter Newgard, p.i.)

Stanford Research Institute has continued efforts in research and development in the transmission of energy across intact skin and in development of a miniature rotary brushless electric motor for use in blood pumps. Increasingly efficient transmission of energy has been achieved across intact skin. Reduction has been achieved in the size of components, both implanted and external. Implanted electronics have been fabricated for sensing the signals from the blood pump through the power circuitry in order to control the implanted pump. The principal accomplishments during this period have included development of a brushless dc motor with efficiency exceeding 30%. This system has been tested on both bench and animal levels. The bench testing has permitted characterization of energy losses of (1) the smaller, more compact, skin transformer; (2) the implanted energy storage and control electronic components; and (3) the motor. Animal tests indicate that the total power input required to operate a complete heart replacement system is approximately 18 watts of electrical energy. Three generations of systems have been developed

and tested during the last contract year. The continuation program will be directed toward further enhancement of operational life and determination of physiologic data for complete system performance under chronic animal test conditions.

STATHAM INSTRUMENTS, INC. Oxnard, California
Contract Amount: $211,853 Contract Number: PH43-68-1502
ENERGY SYSTEM FOR IMPLANTED CIRCULATORY ASSIST DEVICES
(Jack Chambers, p.i.)

Efforts at Statham Instruments, Inc., have been directed toward improving the efficiency and operating characteristics of an implanted, electronically controlled, brushless dc motor. The brushless dc motor is implanted between the two ventricles of a total heart for direct actuation of both ventricles in a manner to control heart rate, stroke volume, ejection waveform, and systolic and diastolic ratios. Evaluation of the entire system has gone through several iterative development stages, testing on the mock loop, and testing in the animal. The animal testing has identified the characteristics of filling and of energy system response to different physiologic demands, including those induced through pharmacologic action. The efficiency of the system has significantly improved over the last contract period through more efficient electronic controls and motor drive circuitry and through reduction of friction in the mechanical power train. Efficiencies in excess of 40% have been measured with the complete system. Prior to initiating animal testing, all total heart units are subjected to up to a hundred hours run in vitro. Several complete implantable energy systems for the total heart have been delivered to the Program Office for test and evaluation. The continuing efforts in this program will be directed toward achieving long-life characteristics within each component, failure analysis of the systems, and upgrading of all components for achieving long-life operation within the animal.

TECNA CORPORATION, Emeryville, California
Contract Amount: $341,033 Contract Number: NIH-71-2035
FABRICATION OF IMPLANTABLE ARTIFICIAL HEART DEVICES
(T. Robinson, p.i.)

Under this contract, Tecna Corporation has developed and fabricated three medical devices in the last year. First, a facility has been developed for the fabrication of clinical-quality intra-aortic balloon catheters for use in conjunction with the Westinghouse console. Fabrication and quality control techniques have been standardized and the capacity now exists for the production of 50 to 100 units per month. Tecna IABs have been extensively tested in other MDAP testing facilities. Second, electromechanical consoles and flexible heart squeezer cups for mechanical ventricular assistance have been designed, fabricated and tested in vivo with satisfactory results. This device has been submitted to IITRI for a screening study. Third, a small, portable, electronically-controlled, volume-limited respirator has been designed and clinical prototypes fabricated. This state-of-the-art respirator will enter initial clinical testing, and formal test and evaluation early in the next year.

THERMO ELECTRON CORPORATION, Waltham, Massachusetts
Contract Amount: $324,840 Contract Number: NIH-71-2065
FABRICATION OF IMPLANTABLE ARTIFICIAL HEART DEVICES
(Walter Bornhorst, p.i.)
This contract has been established to fabricate devices and components in accordance with specifications provided by MDAP. The items fabricated are supplied to a number of MDAP contractors. The fabricated items include the following: blood pump bladders, valves, mock loops for in vitro circulatory support testing, assist pumps, total hearts and extracorporeal bypass pumping systems. A significant portion of the effort was directed toward the fabrication and testing of the veno-arterial bypass system or heart-lung machine. Five heart-lung machines have been delivered for preclinical evaluation at MDAP-sponsored test and evaluation facilities. This effort has capitalized on the latest materials, design, and fabrication improvements developed in other MDAP-sponsored activities. The blood pump fabrication activities include the development of improved flocking techniques, and the development and fabrication of more efficient valve concepts. Next year's work will be similar in scope to that performed during the current year.

THERMO ELECTRON CORPORATION, Waltham, Massachusetts
Contract Amount: $453,905 Contract Number: PH43-67-1116
NEW CIRCULATORY ASSIST DEVICES
(W. Bornhorst and W. Bernhard, p.i.)
Thermo Electron Corporation and Boston Children's Hospital Medical Center have been working together on the development and testing of a left ventricular assist device (LVAD). The LVAD is a 2-valved collapsible bladder blood pump which is interposed between the left ventricular apex and the descending thoracic aorta; it removes blood from the LV chamber during cardiac systole and pumps it into the aorta during diastole, thus maintaining cardiac output while reducing myocardial pressure and volume work. A large body of experimental evidence from calf implantations has been accumulated. In this contract year, there have been four major developments: 1) production of a stable, reproducible LV failure model in the calf; 2) improvement of the device inflow tube design; 3) incorporation of a more durable material (NE 3750 polyurethane) for the pump bladder; and 4) development of a pusher-plate LVAD (H-TAH) which is designed for coupling with implantable power sources. The latter has been demonstrated to function in vivo while being powered by an implantable Plutonium-238 fueled thermal engine. Further physiological studies will be continued to define the interface of mechanical support of circulation and the biological response of animals.

THERMO ELECTRON CORPORATION, Waltham, Massachusetts
Contract Amount: $622,657 Contract Number: PH43-68-1455
DEVELOPMENT OF AN IMPLANTABLE RANKINE-CYCLE CIRCULATORY SUPPORT SYSTEM
(Fred Huffman, p.i.)

The objective of this program is the development of a combined direct-acting energy blood pump system that converts a fraction of the thermal energy from a Plutonium-238 fuel capsule into hydraulic energy that operates an implanted blood pump. The heat produced from the decaying radioisotope is converted into pressure volume energy by means of an electronically controlled vapor cycle engine termed the tidal regenerator engine (TRE). The TRE energy converter is a vapor cycle analog of the regenerative gas cycle converter which combines the advantages of the Rankine engine, (i.e., high pressure differentials for a moderate heat source temperature and small compression work), with the advantageous characteristics of the Stirling engine, (i.e., pressure balance and absence of valves in the conversion cycle). This concept has no sliding surfaces and eliminates the requirement for valves. The system operates at heart beat frequency and is pressure balanced within the system, thereby eliminating any high stress regions in the engine. The system will ignore all signals that may result from premature ventricular contractions unless significant blood is pumped during the contraction. If the natural heart undergoes fibrillation, the implanted circulatory engine system will automatically switch to a fixed internal pumping rate to provide normal cardiac outputs during the period of fibrillation. It will automatically resynchronize upon defibrillation and the appearance of the control signal. Individual subsystems have been designed, fabricated, and tested. Successful in vitro and in vivo tests have been performed with a radioisotope-powered engine circulatory assist system. These tests have yielded promising performance characteristics. Some of the more important milestones achieved include: 1) demonstrated feasibility of heart-sized TRE (actuation rates to 140 BPM); 2) demonstrated engine operation with low power binary solenoid (approximately 210 mw); 3) demonstrated attitude insensitivity of engine; 4) design and fabrication of direct-acting assist pump prototype; 5) compatibility test of thermal energy storage and candidate fuel capsule materials; 6) demonstrated thermal control heat pipe; 7) design and analysis of a 50-watt Pu-238 fuel capsule; 8) preliminary hazards evaluation of Pu-238 fueled, direct-acting system; 9) TRE operation with trifluorephanol working fluid; 10) demonstrated condenser heat rejection through direct-acting assist pump; 11) eighty-hour continuous run of direct-acting system of mock circulatory loop; 12) completion of thermoelectric module design; 13) coupling of power conditioner unit and electronic logic breadboards; 14) breadboard demonstration of electronic logic coupled to engine and sensor (i.e., direct-acting system counterpulsed as a slave to simulated left ventricle); 15) in vivo testing of a totally implanted nuclear blood pump system incorporating a 52-watt Pu-238 fuel capsule. The goal of this program in the coming year is to develop a totally implanted nuclear blood pump system with an operational life of two years. The effort will include engineering development, the implementation of a reliability program, in vivo system tests, and the development of advanced systems concept.

THERMO ELECTRON CORPORATION, Waltham, Massachusetts
Contract Amount: $294,718 Contract Number: NIH-69-2182
NEW CIRCULATORY ASSIST DEVICES
(W. Bornhorst and W. Bernhard, p.i.)
Under this contract, Thermo Electron and Boston Children's Hospital Medical Center have developed a Bilateral Circulatory Assist system. The right assist device pumps blood from the right ventricular infundibulum to the pulmonary artery; the left assist device (the LVAD developed under Contract Number PH-43-67-1116) pumps blood from the LV apex to the descending aorta. When both devices are simultaneously operating, the entire circulation can be supported. Extensive engineering, physiological and hematological evaluations have indicated that the system is very workable. Calves with severe induced left ventricular failure have been maintained with near normal hemodynamics. Animals with ventricular fibrillation have also been studied. The most significant result to date has been the survival of a bilateral system recipient calf for 17 1/2 days of induced ventricular fibrillation. The experiment, which represents the longest period of total functional mechanical cardiac replacement yet observed, had to be terminated due to the progression of pneumonia which was present at the time of implantation. The function of total heart support will be further investigated through the implantation of mechanical left and right hearts with the natural hearts remaining in place. These efforts are expected to define the response of the lung to different modes of right heart assist pumping.

THERMO ELECTRON CORPORATION, Waltham, Massachusetts
Contract Amount: $50,200 Contract Number: PH43-66-982
EFFECTS OF INTRACORPOREAL HEAT AND RADIATION
(Fred Huffman, p.i.)
The feasibility of totally implantable blood pumps depends upon the ability of the body to dissipate the reject heat from the power source which drives the pumps. If the energy source is a radioisotope, the body must also tolerate chronic intracorporeal radiation. The objective of the endogenous program is to study the effects of intracorporeal radiation and waste heat upon mammals. This program arose from canine studies which used heat exchanges energized by (1) 16-24-watt Plutonium-238 capsules, by (2) radiation equivalent sources which simulate the neutron and gamma radiation of a 24-watt Plutonium-238 heat source without producing the heat, and (3) by implantation of an electrically energized heat source of 50 watts using a functioning left ventricular assist pump as a blood cooled heat exchanger. The work effort of the contract year lead to the definition of the location, suspension, surgical procedure, and postoperative care for implantation of the first nuclear heart assist pump system in a calf. This system has a weight of approximately 11 pounds and a volume of approximately 3 liters. Such devices have been tolerated for periods of up to three weeks and have shown at autopsy no evidence of adverse reaction to the added heat. In experimentation with radiation equivalent sources in primates, the capsules have been implanted retroperitoneally and suspended from the psoas tendon. Studies indicate that three such primates are in good condition at periods up to one year, in spite of the nuclear radiation and the relatively large size of the capsule. In addition, dogs bearing such capsules implanted in the preceding contract years

have continued to be maintained and monitored physiologically. The temperature, weight, and hematologic and metabolic data have remained within normal limits. Work will continue during the coming year with the long range objective of maintaining a colony of animals with implanted radioisotope sources to establish more fully the safety guidelines.

TYCO LABORATORIES, INC., Waltham, Massachusetts
Contract Amount: $97,590 Contract Number: NIH-69-32
DEVELOPMENT OF AN IMPLANTABLE BIOLOGICAL FUEL CELL
(Jose Giner, p.i.)
The present program at Tyco is concerned with parametric studies of biological fuel cell performance. A fuel cell has been designed and fabricated using thin film, printed circuit techniques which will permit easy interchange of replaceable electrode and membrane components. Performance data have been obtained for in vitro and in vivo operation for prototype, thin, single-cell units. The influence of such factors as reactant concentration and flow velocity have been examined in vitro using buffered saline solutions containing 90 mg% glucose as the perfusion medium. Under in vitro conditions the maximum fuel cell power output has been approximately 0.1 milliwatt/cm^2 using Pt as the electrocatalyst and Cuprophane and dimethylsilicone-polycarbonate membranes for fuel and oxygen extraction, respectively. Preliminary in vivo test results using the fuel cell in an extracorporeal bypass with a sheep as the test animal produced an initial power output of 2 milliwatts for electrodes of 50 cm^2 active area, or a power output density of 0.04 milliwatt/cm^2. However, the anode potential undergoes a degradation process which reduces overall cell potential gradually during operation. There are a number of possible mechanisms for this phenomenon which will be examined in further study. The cathode, on the other hand, maintains a normal potential throughout the testing period of hours without degradation at current densities as high as 0.5mA/cm^2. During the next year, additional in vivo tests are planned with cells incorporating detailed refinements, in an effort to elucidate electrode processes at the anode, to increase the operating efficiency, and to demonstrate long-term performance.

UNIVERSITY OF MINNESOTA, Minneapolis, Minnesota
Contract Amount: $19,992 Contract Number: PH43-67-1122
BLOOD FLOW THROUGH BLOOD PUMPS AND VALVES
(P. Blackshear, p.i.)
Since 1967 this group has been studying the fluid dynamics of blood flowing in small tubes. Their activities and findings to date include: (a) the hemolysis which occurs in small tubes was found to result from entrance phenomena and separated flow; (b) ghost cells were obtained by improved techniques for the measurements of velocity profiles in small channels; (c) cell wall interactions were found to be increased by hematocrit, flow velocity and platelet count as measured by Attenuated Total Reflectance (ATR) microscope; (d) a 3-D microscope was developed and calibrated in combination with a computer program for the measurements of shear rate, cell density distribution and three dimensional velocity vectors in a flow system; and (e) the surfaces of cell and protein depositions were analyzed by scanning electronmicroscopy. This contract terminated January 6, 1972.

UNIVERSITY OF MISSISSIPPI MEDICAL CENTER, Jackson, Mississippi
Contract Amount: $20,756 Contract Number: PH43-67-1118
DEVELOPMENT OF A LEFT VENTRICULAR ASSIST DEVICE
(T. Akutsu, p.i.)
A V-shaped implantable series-type device with an air-driven outlet valve has been constructed and implanted in animals. The volumes of two sizes of this device are 65 and 95 ml, respectively. The control system for this series-type device has a rate compensation circuit which can automatically change the systole-diastole ratio with changes in pulse rate. A control system which can be used for either the bypass-type device or the in-series type allows pumping once every 2nd to 8th trigger, and can adjust the number of functioning chambers from 6 to 3. It was decided by the Program Office that the development of this assist device had reached a point at which further funds for development were not warranted. Further work on the control system was transferred to another contract under Dr. Akutsu's direction. This contract terminated February 29, 1972.

UNIVERSITY OF MISSISSIPPI, Jackson, Mississippi
Contract Amount: $142,042 Contract Number: NIH-69-2185
DEVELOPMENT OF A SILASTIC TOTALLY-IMPLANTABLE HEART
(T. Akutsu, p.i.)
The design of the four-chambered Silastic totally-implantable heart with integrally molded valves which was developed in the preceding contract year has been finalized. The inlet valve is monoleaflet and elliptical-shaped, and the outlet valve is a low-resistance, bicuspid type. The average survival time in in vivo experimentation with the prosthetic heart has increased from 29 hours in the previous contract year to 99 hours in the present contract year. Hemodynamic characterization of the prosthetic pump performance is as follows (measurements that are reported are typical): cardiac output is 10 l/min, RAP and LAP = 0, PAP = 20 to 30 mmHg, and mean arterial pressure 120 to 150 mmHg. Cardiac output and arterial blood pressure stay constant at this level until the terminal event. Physiologic characterization of the test animals is as follows: plasma free hemoglobin reaches a peak of about 120 mg% immediately following extracorporeal circulation and then decreases to 40 mg%. Platelets remain about 300,000, fibrinogen is at a level of 400 to 600 mg% (normal is 200 to 400 mg%). Arterial saturation is easily maintained at 98% with a pO_2 in the range of 100 to 200 mmHg and a pCO_2 from 40 to 50 mmHg. Bicarbonate is used if necessary to maintain the pH between 7.4 and 7.5. Urine output averages between 3 and 4 liters per day. Renal function remains good on the average but BUN rises from 20 to 80 as part of the complex series of changes that accompany the terminal events. There is no problem with maintaining a normal electrolyte balance. Pathologically the kidneys show small patchy infarcts of a diameter of usually less than 1.5 cm. The lungs are found to be congested, and there is usually some patchy atalectasis; however, inflammation is minimal and there is no hyaline membrane formation. The marked increase in survival time has served to make several problems clear. Among these are the apparent limitations in a prosthetic device made of silicone rubber (due to its short flex life) and the problem of infection, which becomes major after one week of survival. In addition to overcoming these two limiting problems, the objectives of the future work are to accumulate and

analyze pathophysiologic and histological data and to further define the capability of supporting life with a totally-implantable prosthetic heart.

UNIVERSITY OF UTAH, Salt Lake City, Utah
Contract Amount: $60,000 Contract Number: NIH-69-2181
ARTIFICIAL HEART WITH INTRINSIC CONTROL
(W. J. Kolff, p.i.)

During the present contract year physiologic experimentation with two different types of prosthetic hearts was performed. A hemispherical diaphragm type of prosthetic pump, labeled the Kwan-Gett heart, has proven to be a reliable, strong, easily fabricated pump. In addition, work was initiated with a spherical shaped bladder prosthesis labeled the Donovan pump. With each type of pump, evaluation of several different types of blood-contacting surfaces and inflow and outflow valves was performed. At this point it appears as though a rough-surfaced intima with a build-up of fibrin is more promising than an entirely smooth surface and the most promising type of valve appears to be the Bjork-Shiley prosthetic aortic valve. The design of the previously-used Kwan-Gett hearts has been altered so that the base diameter which was previously 7 cm has been increased to 8 cm; this was done to obtain a larger cardiac output. During this past year several total heart implantations in calves were done with resulting survival time in excess of one week. Among these was an experiment in which the survival time was 14 days and 2 hours. The achievement of the prolonged survival time has enabled this group to study the physiologic effects of prosthetic device pumping uncomplicated by those of the post-surgical state. The following problems have become apparent: thrombosis and clotting remain central to the question of artificial heart implantation. In experiments in which an artificial intima of woven Dacron cloth was used, there was consistently minimal evidence of thromboembolism. Hemolysis appeared to be a major problem with the Dacron cloth intima. The hemolysis leads to hemoglobinuria and, if allowed to persist, also leads to formation of tubular casts and renal failure. It may also be responsible for liver failure. Pulmonary problems still remain among the most important to the field of artificial heart implantation. Pulmonary insufficiency secondary either to simple congestion or to edema and shunting without congestion occur as two distinct patterns. It is felt by this group that the pulmonary problems may result in part from a disseminated intravascular coagulopathy. The hematologic data are inconclusive at this point and will be a major focus for further study in the coming year.

WESTINGHOUSE ELECTRIC CORPORATION, Pittsburgh, Pennsylvania
Contract Amount: $124,892 Contract Number: PH43-67-1139
DEVELOPMENT OF AN INTRA-AORTIC BALLOON ASSIST DEVICE
(J. Evans, p.i.)

With support of this contract, Westinghouse has continued to develop an electromechanical console for intra-aortic balloon pumping. Model IV consoles underwent extensive engineering and biologic evaluation at the IITRI T & E facility, and they were thought to be suitable for initial clinical trials. Several significant modifications to the Model IV design were made, and

twenty-two Model IV consoles were refitted to Model V specifications. The modifications include a closed-volume pumping system with automatic start-up, automatic recharging and leak detection capability. The Model V design, which is thought to be safer and much easier to use than the Model IV, has been submitted to IITRI for screening test and evaluation. Fiscal Year 1972 was the final year of active developmental work on the Westinghouse system. It is anticipated that within FY 1973, initial clinical trials of the Westinghouse system (together with the balloon/catheter produced by Tecna Corporation) will be undertaken in patients with post-myocardial infarction cardiogenic shock.

YALE UNIVERSITY, New Haven, Connecticut
Contract Amount: $47,412 Contract Number: NIH-72-2901
SEQUENCED PULSATION IN THERAPY OF CARDIOGENIC SHOCK
(L. Cohen, p.i.)

This contract continues work begun under contract number NIH-71-2069 with Hamilton Standard; the same research team is involved (see above). Two Sequenced Pulsation Devices, Model IIa, will be fabricated and subjected to physiological evaluation. This is a refinement of the earlier system in that it includes an active vacuum chamber and improved controls. Three testing phases will be carried out, including, first, tests on normal human volunteers and second, on patients undergoing diagnostic cardiac catheterization. If results from the first two phases are promising, initial trials of the Sequenced Pulsation Device will be undertaken in therapy of patients with post-myocardial infarction cardiogenic shock. Simultaneously, additional units will be fabricated for formal test and evaluation at a MDAP Test and Evaluation facility.

ARTIFICIAL LUNG

The Medical Devices Applications Program supports the development and improvement of new or improved blood oxygenators for short-term use in presently existing extracorporeal perfusion systems for open heart surgery, and for long-term extracorporeal perfusion to support the failing cardiopulmonary system. The concepts which have been supported are those which eliminate the blood-air interface, which has been shown to damage blood by denaturation of blood proteins and destruction of cellular elements, and to replace it with a liquid/liquid or a blood-membrane interface. During the course of this program, concepts have been supported in which oxygenators have been fabricated from materials that are more thrombo-resistant, and attempts have been made to improve the hemodynamic design of blood oxygenators in an effort to reduce thrombus formation further by eliminating areas of stagnation and turbulent blood flow. During this contract year efforts have been directed toward developing materials that meet the specifications with regard to gas transfer and thrombo-resistance and are inexpensive to produce, so that when oxygenators are finally fabricated from these new materials they will be competitive from a cost standpoint. During the past year the MDAP has supported oxygenator development in the following areas: 1) Liquid/liquid interface oxygenators; 2) Capillary membrane oxygenators; 3) Combination pump-oxygenators; and 4) The development of ultrathin membranes.

AMICON CORPORATION, Lexington, Massachusetts
Contract Amount: $13,862 Contract Number: NIH-71-2367
FEASIBILITY STUDY OF THE USE OF POLYSULFONE IN OXYGENATORS
(Robert A. Cross, p.i.)

The Amicon Corporation has undertaken a feasibility study to determine if a hollow fiber oxygenator based on an asymmetric membrane is feasible. To date, asymmetric follow fibers have been made from polyvinyl cloride and polysulfone polymer with the "skin" on the inside surface. The skin is probably microporous with pores in the 200 Å diameter range, but the hydrophobic nature of the polymers prevents liquid water from penetrating into the membrane producing a large gas diffusional resistance. The "gas to gas" permeability of these membranes is higher than that of a 2-mil Silastic membrane for both CO_2 and O_2, and there is no apparent penetration of plasma into the membrane at transmembrane pressures up to at least 760 mm/Hg. Experiments conducted with water flowing on the inside of the fibers and with pure oxygen at a slightly lower pressure on the outside of the fibers have given oxygen transfer rates ranging from 43 to 65 cc/M^2-min, which are values of the same order of magnitude as theoretical values calculated assuming no membrane resistance. The principal advantage of the asymmetrical fiber would be cost. It is not planned to continue this contract beyond the current contract period.

BROWN UNIVERSITY , Providence, Rhode Island
Contract Amount: $86,853 Contract Number: NIH-69-2047
TESTING AND EVALUATION OF BLOOD OXYGENATORS
(Pierre M. Galletti, p.i.)

This program was initiated to evaluate and compare various oxygenators being developed by contractors to the MDAP Program. This program has used a three prong approach; 1) evaluation of gas transfer capacity in membrane oxygenators under standardized conditions; 2) engineering evaluation of flow dynamics and flow distribution to identify the causes of sub-optimal performance; and 3) biological evaluation of damage associated with blood circulation through the oxygenator, as ascertained from the study of the blood of the test animal (formed elements and coagulation system) and of target organs such as the natural lung. The study involves the oxygenator as well (detailed autopsy of artificial lung following performance evaluation). Under this contract the gas-to-gas transfer method has been developed which allows the resistance to gas transfer across the membrane to be evaluated. A gas-to-water transfer test has also been developed which allows an investigation of the transfer performance of an oxygenator purely as an exchange device. During the past contract year these tests for evaluation of oxygenators have been further refined and applied to the testing and evaluating of membrane oxygenators. Brown University has continued to test and evaluate the Dow hollow capillary oxygenator in both the 1L and 3L/min rated sizes, the General Electric-Peirce oxygenator, the Landé-Edwards oxygenator and the Sci-Med Spiral Coil oxygenator. Studies have also continued upon the hematological system of the sheep, particularly with regard to coagulation. A limited number of long-term partial perfusions have been performed with selected oxygenators. It is planned to continue work of this type with more emphasis on long-term perfusion.

DOW CHEMICAL COMPANY, Walnut Creek, California
Contract Amount: $144,235 Contract Number: PH43-68-1387
DEVELOPMENT AND EVALUATION OF NEW AND IMPROVED OXYGENATOR
(Frank W. Mather, p.i.)

This contract, which is in the fourth year, has progressed to the point that a hollow fiber membrane oxygenator is now undergoing clinical evaluation. Even though a unit has been developed which is being used for clinical application, a number of areas still require considerable development. To date, the units for clinical application have been fabricated from General Electric's poly-carbonate-siloxane copolymer, but there is much concern with respect to the long-term use of this copolymer because of copolymer availability and the additional problem of broad variations from one batch of polymer to another with respect to physical and mechanical properties. During the past year substantial progress has been made on the development of the polystyrene-siloxane copolymer as a potential alternative to the polycarbonate-siloxane copolymer. Polystyrene also offers the additional desirable characteristic of being ethylene oxide sterilizable. At this time last year the testing of the 1L/min units had begun at the test and evaluation center at IITRI and scale-up to the 3L/min unit was underway. Since that time the fabrication of the 3L/min units has become routine, and efforts have moved to scaling-up to the 6L/min units. Minor modifications have been made with regard to the central distributing

manifold for oxygen, the placement of supports in the fiber bundles, and the addition of molded lucite jackets with screw end caps and molded high density polyethylene headers. A centrifugal potting technique for forming the tube sheet of the blood oxygenators has been developed, using low viscosity polyurethane polymers. This technique has been developed to a point at which it can be brought on line for routine production within a two month period, once the final material for spinning of the fibers has been chosen. Approximately 30 4-hour total cardiopulmonary bypass experiments were conducted at IITRI using calves and, on the basis of these studies, it was decided that clinical trials should be initiated. More than 20 successful clinical perfusions have been carried out using 2 3L/min oxygenators in parallel. As part of the preparation for preparing oxygenators for clinical trial, a class 100 clean room was set up with laminar air flow hoods, and all fabrication is carried out in this room. Dr. Dutton and Dr. Edmund at the Cardiovascular Research Institute have continued to carry out studies quantitating thrombus formation in hollow fiber devices and to study the operating parameters of the device in rhesus monkeys. These studies are in preparation for use of the Dow oxygenator clinically in newborns requiring definitive repair of congenital malformations of the heart. This contract will be continued, and will include work previously performed under two other Dow contracts, NIH-71-2360 and NIH-71-2368.

DOW CHEMICAL COMPANY, Walnut Creek, California
Contract Amount: $50,000 Contract Number: NIH-71-2360
FABRICATION OF OXYGENATORS USING SPECIFIED MATERIALS
(Frank Mather, p.i.)
This contract supports (1) the development of the spinning technology necessary to spin hollow fibers and (2) fabrication of oxygenators from promising materials as specified by the Medical Devices Applications Program.

During the course of this contract, techniques have been developed and fibers have been spun from a solution of a copolymer consisting of 50% polysulfone and 50% siloxane. Spinning fibers from solution is a laborious procedure, and it is felt not to be adaptable to commercial production of oxygenators. Efforts are under way to alter the physical properties of this copolymer so that it may be spun using a melt extrusion system. Although this material can be spun into hollow fibers and has suitable gas-transfer characteristics, it is not being considered strongly as an alternative material at this time.

A second copolymer, consisting of 50% polystyrene and 50% siloxane, has also been extruded into hollow fibers. Oxygenators have been fabricated from these fibers and have undergone in vitro evaluation. Although this material offers some promise as an alternative substance and can be ethylene oxide sterilized, it has the fault of poor tensile strength when spun into hollow fibers. Efforts are presently under way to increase the tensile strength.

Oxygenators have also been fabricated under this contract for evaluation of surface coatings. Work is presently under way with two other MDAP contractors to evaluate the possibility of applying hydrogel coatings inside hollow fibers. Several oxygenators have also been fabricated under this contract

and supplied to other MDAP contractors to support work in other areas.

It is not planned to continue this contract. The work will be transferred to Dow Contract PH43-68-1387 (see above).

DOW CHEMICAL COMPANY, Walnut Creek, California
Contract Amount: $34,645 Contract Number NIH-71-2368
THE DEVELOPMENT OF A CAPILLARY OXYGENATOR
(Frank Mather, p.i.)

Work under this contract lies in two areas. The first is concerned with development of a centrifugal method of production of the end tube sheet of hollow fiber blood oxygenators. Although silicone rubber has heretofore been used for this, there are drawbacks. These are: (1) it is expensive and (2) it is inherently a weak material which allows the end tube sheet to flex at high perfusion pressures. Techniques have been developed to use low viscosity polyurethane resins for this purpose. This has been developed to a point at which it can be readily integrated into a routine fabrication process.

The second area of work under this contract has been the development of a hollow-fiber blood oxygenator with blood on the outside of the fibers and gas inside. Currently, Dow is using a modified Leesona winder to orient hollow fibers accurately in parallel fashion. Several such oxygenator units have been made and evaluated in vitro. These evaluations suggest that this design serves more effectively for oxygen and carbon dioxide transfer than does the design with blood within the hollow fibers and oxygen outside. Studies continue to permit such choices as fiber size, fiber spacing, and winding tension. It is anticipated that in vivo studies will be initiated shortly. This contract will not continue after the end of the current contract period. The work will be transferred to Dow Contract PH43-68-1387 (see above).

ESSO RESEARCH AND ENGINEERING COMPANY, Linden, New Jersey
Contract Amount: $97,075 Contract Number: NIH-71-2369
EXAMINATION AND EVALUATION OF FLUOROCARBONS FOR USE IN LIQUID MEMBRANE OXYGENATORS
(William J. Asher, p.i.)

A liquid-liquid interface has been explored as a means of blood oxygenation. For this purpose, bubbles of oxygen in fluorocarbon are allowed to rise through the blood to be oxygenated. Initial exploratory work has been encouraging with regard to transfer of oxygen and carbon dioxide and with regard to absence of apparent blood damage.

During the year work was performed on the evaluation of fluorocarbons for the physical properties which might allow them to be used in this fashion. Uneasiness concerning compatibility with blood led to the fabrication of an interface generator capable of generating a continually renewing blood fluorocarbon interface.

Work with regard to blood compatibility has involved several areas: (1) development of an analytical procedure to detect trace levels of fluorocarbon in blood and other body fluids; (2) the possibility of lipid extraction from blood by fluorocarbon (there was no extraction by one tested fluorocarbon); and (3) measurement of osmotic fragility of red blood cells after contact with fluorocarbon (no change with one fluorocarbon tested). After 24 hours of constantly renewing contact with fluorocarbons, there appeared to be a slight depression in prothrombin level, but not out of the limits of normal.

The research plan for the coming year involves primarily the solution of further problems in biocompatibility.

GENERAL ELECTRIC COMPANY, Schenectady, New York
Contract Amount: $29,300 Contract Number: NIH-71-2361
FABRICATION OF OXYGENATORS USING SPECIFIED MATERIAL
(William Matthewson, p.i.)
This contract was funded in an effort to use the General Electric-Peirce oxygenator as a test vehicle for some new materials and surface treatments being developed in the MDAB program. Progress on this contract has been slow for several reasons. General Electric Company is in the process of redesigning the General Electric-Peirce oxygenator, and it was decided to await the completion of this new design before attempting to incorporate new materials into the oxygenator. Work has been slowed by the difficulty in finding suitable methods for applying the cone field to the membranes which are an integral part of the General Electric design. A suitable support material has been found for the ultrathin membranes, and it is anticipated that within a very short time some General Electric-Peirce oxygenators will be fabricated using supported ultrathin membranes. Work is also under way for the development of techniques for applying hydrogels to the surface of a polycarbonate siloxane membrane. As soon as this technique is perfected, membranes of the General Electric-Peirce oxygenator will be coated with hydrogels and undergo in vivo evaluation. Other surface treatments and materials are under consideration for incorporation into the General Electric-Peirce oxygenator for evaluation. The extent of future work under this contract is currently under evaluation.

GEOMET, INC., Rockville, Maryland
Contract Amount: $98,250 Contract Number: NIH-71-2432
SYSTEMS ANALYSIS FOR RESPIRATORY DEVICES
(Elliot Z. Ratner, p.i.)
A systems analysis for respiratory device development was made consisting of the following three study areas: (1) the medical conditions and problems associated with the function of the respiratory system, (2) a review and analysis of existing and potential respiratory devices, and (3) an analysis of the social and economic benefits to the nation through the utilization of respiratory devices. Based upon the results of the systems analysis study, recommendations and priorities for the establishment and management of a research and development program for respiratory devices were proposed. Epidemiologic data indicated that from a cost/benefit point of view the population between 45 and

64 years of age was most affected by pulmonary disease. It is estimated that two to three billion dollars of lost income is incurred by the partially and completely disabled people suffering from chronic obstructive lung disease and pneumoconioses. In addition, lung cancer and chronic obstructive lung diseases annually deprive the nation of a life expectancy of 180,000 man years.

An analysis of demographic, morbidity, and mortality data of the population affected by pulmonary diseases, combined with analyses of existing respiratory devices and the findings drawn from a respiratory intensive care unit survey, resulted in the following recommendations: national centers for respiratory device testing and evaluation should be established and, in addition, an advisory commission to assist in the development of device standards should be established.

It was also proposed that once these recommendations have been instituted the following specific projects be undertaken: (1) A program designed to determine design specifications and to test and evaluate personal and area protection systems for the purpose of prevention of lung disease; (2) A program designed to result in adaptively preprogrammed respirators that are able to adjust to the ventilatory needs of patients; (3) A program of research and development of various auxiliary lung devices (various design configurations and the test and evaluation of them under clinical conditions should be closely followed and supported); and (4) A program to design with current technology less expensive body plethysmographs, mass spectrographs, gas chromatographs, and improved oxygen and carbon dioxide electrodes.

This analysis indicated that the rate of patient survival in specific respiratory care units is greater than in other intensive care units which provide services for similar disease conditions. The success of these units seems to be directly attributable to the staff personnel training, the roles played by various personnel, and the 24-hour coverage and other patient services provided. The longer the unit has been in operation the greater the success seems to be. It is concluded that the knowledge and experience which have been developed in the more successful respiratory care units should be made readily available to others. This contract terminated February 29, 1972, and a detailed report will be made available.

INTERNATIONAL BUSINESS MACHINES Corp. Gaithersburg, Maryland
Contract Amount: $114,718 Contract Number: NIH-71-2431
SYSTEMS ANALYSIS STUDY FOR RESEARCH AND DEVELOPMENT OF RESPIRATORY DEVICES
(R. Bartlett, p.i.)
A systems study to identify unfulfilled device and instrumentation requirements in the field of pulmonary medicine and to generate device development plans appropriate to these requirements was completed. The data base of the analysis involved a survey of the characteristics, diagnostic and therapeutic features, epidemiology, and facilities for care of various respiratory diseases. A survey also was made of devices, which characterized physical principles, conditions for use, significant medical and engineering features, and economics.

The epidemiologic data indicated that the major focus of the study should be chronic obstructive lung diseases in patients above 45 years of age, pneumoconioses, neoplasms of the lung, and acute pulmonary failure. The analysis considered not only the most important diseases and the devices with the potential for impacting these diseases but also the factors which would affect eventual use of the device. These included the potential benefits to be derived from such usage, the acceptability by both the patient and the medical community, and the feasibility of developing the device.

This systems analysis resulted in a development plan for five top priority devices. These included: (1) nonslip tubing connectors for patients requiring mechanical ventilation; (2) X-ray image roentgenology to denote areas of unusual film density patterns that may not be recognizable by the unaided eye; (3) an oxygen flow monitor to control carefully the inhaled oxygen concentration; (4) an atraumatic tracheostomy cuff; and (5) a small airways restriction detector.

In these development plans the report presents the basic concept behind each device, the development problems, and the projected costs and time involved. This contract terminated January 29, 1972. A detailed report will be available.

MEDI-PHYSICS, INC., Emeryville, California
Contract Amount: $67,816 Contract Number: NIH-71-2363
DEVELOPMENT OF A PUMP OXYGENATOR
(Harry S. Winchell, p.i.)
The aim of this program was to develop a membrane oxygenator in which pulsations in the pressure of the oxygenating gas mixture might serve to pump as well as to oxygenate the gas on the other side of a flexible membrane. Multiple pump oxygenator units were assembled until a model was achieved which proved leak-free.

The final pump oxygenator was capable of pumping as much as 6 liters a minute, but could transfer no more than 50 ml per minute across the membrane. This observation led to redesign of the apparatus, which is presently in final assembly. The extent of future work under this contract is under evaluation.

NORTH STAR RESEARCH AND DEVELOPMENT INSTITUTE, Minneapolis, Minnesota
Contract Amount: $38,326 Contract Number: NIH-71-2364
PROVIDE ULTRATHIN MEMBRANES FOR EVALUATION IN BLOOD OXYGENATORS
(Lee T. Rozelle, p.i.)
Ultrathin membranes are prepared by a flow-casting procedure developed at North Star Research and Development Institute in earlier membrane research programs. To fabricate ultrathin membranes, a polymer is dissolved in a solvent or combination of solvents to form a casting solution. This viscous casting solution is then placed in a hopper above a tank of water, and allowed to flow through a slit orifice at the bottom of the hopper and down an inclined plate glass onto the water surface. There, the solution spreads spontaneously

over the water surface. A gelled polymer film is formed as the solvent dissolves in the water and evaporates in the air. The film is drawn away from the point of formation at a controlled rate by means of a wind-up roller at the opposite end of the tank of water. During the first eight months of this program, gas permeable membranes had been fabricated from several polymers, including silicone-polycarbonate copolymer, plasticized cellulose, silicone oil-modified trimethylsilyl cellulose, and to a preliminary extent, dimethyl silicone rubber. Fluorosilicone membrane fabrication attempts have so far been unsuccessful. Most other polymers such as polysulfone do not have sufficient gas permeability even in the ultrathin state to be considered. In addition, considerable program effort had to be diverted to a search for a suitable, low-cost membrane support that would meet requirements for blood oxygenator design such as the General Electric-Peirce oxygenator. The final task involved the fabrication and lamination of these membranes onto suitably embossed Tyvek supports for fabrication in the General Electric oxygenator. The extent of future work under this contract is currently under evaluation.

TECNA CORPORATION, Berkeley, California
Contract Amount: $104,500 Contract Number: NIH-71-2430
SYSTEMS ANALYSIS STUDY FOR RESPIRATORY DEVICES
(S. Kitrilakis, p.i.)

A systems analysis was performed to define device concepts which can have significant impact on the morbidity and mortality associated with pulmonary disease. These concepts were drawn from an analysis of epidemiologic data, a review of the relevant literature, interviews with medical consultants at the Cardiovascular Research Institute of the University of California Medical Center and pulmonary specialists in other centers, and recommendations from physical scientists on the faculty of the University of California at Berkeley. The primary emphasis was placed on chronic obstructive lung disease (including asthma, bronchitis and emphysema), respiratory neoplasms, and acute respiratory failure. From existing epidemiologic data and trends, projections are made for morbidity and mortality in the year 1977. Chronic obstructive lung disease accounts for the bulk of disability and mortality; 3,000,000 persons will be limited in activity and almost 500,000 persons hospitalized in 1977. More than 2/3 of these patients will be under the age of 65. More than 80,000 deaths will result from chronic obstructive lung disease in 1977. Malignant neoplasm of thoracic organs will cause the death of about 100,000 persons in 1977. About half will be younger than 65. Acute respiratory failure will seriously threaten the lives of over 250,000 with a mean age in the late 40's. Of these 250,000 patients, more than 200,000 will have had previously normal or nearly normal respiratory function prior to the episode of acute respiratory failure. Deaths caused by acute respiratory failure in 1977 will amount to nearly 70,000.

Despite the extreme diversity of etiology, natural history, and symptoms among these pulmonary diseases, they share a number of common anatomic and functional abnormalities on the one hand and therapeutic modalities on the other. The basic measurements performed in functional assessment involve gas flows, volumes and concentrations. Devices used in the treatment of

both chronic obstructive lung disease and acute respiratory failure are intended to provide functional support or temporary replacement of pulmonary function.

Analysis of these factors produced a list of needs for new devices and this list was then examined with respect to cost/benefit, patient acceptability, acceptability by the medical community, development feasibility, and useful life. Among those device concepts recommended for top priority development are the following: (1) improved X-ray resolution of soft tissue, (2) non-invasive blood gas measurement, (3) improved methods for respiratory flow measurement and respiratory gas composition determination, (4) microwave scanning for fluid distribution in lung tissue, and (5) the monitoring of breathing rate by acoustic techniques. It is believed that the development of each of these devices is possible with application of existing technology or with some moderate extension of existing technology.

The development of a totally implantable artificial lung was given low priority because it would require new technology of only moderate acceptance, be excessively expensive, and be of potential benefit to relatively few patients. This contract terminated February 22, 1972. A detailed report will be made available.

UNION CARBIDE CORPORATION, Bound Brook, New Jersey
Contract Amount: $94,942 Contract Number: NIH-71-2365
FABRICATE OPTIMIZED TEMPLATES AND STUDY BLOOD FLOW THROUGH A SHORT PATH MEMBRANE BLOOD OXYGENATOR
(Mark A. Spivack, p.i.)

Union Carbide was funded to conduct a feasibility study of an oxygenator in which membranes separate 1-mm-long channels for blood and oxygen of microscopic diameters. A configuration was obtained in which blood flows in fine channels 15 to 50 micra in diameter through a plate in which the oxygenating gas passes through finer channels surrounding the blood channels. An oxygenating plate was fabricated with up to 50,000 blood channels/cm^2, capable of oxygenating several cc of blood/cm^2/min. with a pressure drop of about 1 mmHg.

The sheet is manufactured in the following steps: (1) generation of an element template, (2) coating of the template with membrane material, (3) mounting of the coated template element in a combined supporting-manifolding frame, (4) removal of the template by digestion or solution, and (5) stacking and manifolding of the individual elements into an assembled oxygenator. Sufficient problems have been encountered in forming the templates from a satisfactory material to indicate that successful development of this oxygenator is unfortunately unlikely. It is planned that this contract will terminate at the end of the current contract period.

WASHINGTON UNIVERSITY, Saint Louis, Missouri

Contract Amount: $21,567 Contract Number: NIH-71-2366

DEVELOPMENT OF A CENTRIFUGAL FLUOROCARBON BLOOD OXYGENATOR

(Edmund E. Spaeth, p.i.)

The objective of this contract has been to investigate the concept of contacting venous blood with an immiscible, oxygen-bearing fluid (fluorocarbon) in the presence of a centrifugal field so as to maintain complete, controlled separation of the two phases during the gas exchange process. This system offers the following advantages: (1) very small priming volume, (2) no direct blood gas contact, (3) no membrane diffusional resistance, and (4) use of the fluorocarbon as both a gas-exchange and heat-exchange surface. During the period of this contract the centrifugal fluorocarbon oxygenator (CFO) system has been fabricated and operated to demonstrate the complete separation of fluorocarbon from deionized water for a range of flow rates from 40 to 275 ml/min at rotational speeds greater than 150 rpm. This is equivalent to over 4L/min in a 1 M^2 contact area device. Both co-current and countercurrent flows have successfully been demonstrated. As part of bringing the CFO system to an operational status and using it in experiments, a number of design improvements have been made. Experiments are currently under way to evaluate the transfer rates of oxygen and carbon dioxide in this oxygenator, and in vivo experiments are planned. At the present time no data are available with regard to blood trauma in this device. It is expected that sufficient data will be collected to demonstrate feasibility. Further support for this contract is not planned in advance of assay of biocompatibility of the fluorocarbons.

BIO-INSTRUMENTATION

Long range requirements of the MDAP for instrumentation include a wide and sophisticated variety of devices and systems for carrying out diagnostic and monitoring functions on the physiologic state of the patient and the physical state of the medical device, for effecting control of a process or device, and for taking corrective or therapeutic action when required. The equipment involved may range from highly miniaturized, body-compatible, implantable devices to large systems which employ computer and signal processing techniques to reduce, process, store and display the data acquired from the primary sensors or transducers. Instrumentation for preventive applications may include detection and warning devices or prophylactic devices which serve to minimize or forestall the occurrence of adverse physiologic conditions. Effort during the past year has been limited to the continuation of several development programs already under way. These have included the development and improvement of blood pressure transducers, methods for measuring and monitoring arterial oxygen levels and serum enzyme levels, a gel method for detecting creatine phosphokinase (CPK), chemical sensors for measuring blood constituents in vivo, and a system for non-invasive diagnostic analysis of acoustic signals from implanted blood pumps or heart valves or from the cardiovascular system. In the Spring of 1972 a Request for Proposal on Instrumentation was issued. The 117 proposals received are being reviewed, and contracts will be awarded early in fiscal 1973.

THE FRANKLIN INSTITUTE RESEARCH LABORATORIES, Philadelphia, Pennsylvania
Contract Amount: $8,700 Contract Number: NIH-69-2237
DEVELOPMENT OF SENSORS TO MONITOR BLOOD CONSTITUENTS IN VIVO
(Paul L. Kronick and Harvey Scott, p.i.)

The objective of this program was the preparation and testing of insertable sensors for blood-plasma ions based on lipid bilayer elements. Self-supporting bilayers held in ca. 1 mm^2 plastic frames, prepared according to the procedures of Mueller and Rudin from sphingomyelin/tocopherol and n-decane/oxidized cholesterol, were investigated. Reinforcing media were sought in which to imbed the bilayers to compensate for mechanical fragility. However, as with hydrogel supports of agarose and polymerized 2-hydroxyethl- and 2,3-dihydroxypropylmethacrylates investigated in the first year of this program, bilayers broke in the course of polymerizing or forming a polyacrylamide hydrogel support. Replacing the hydrogel with liquid glycerol provided mechanical support, but destroyed the valinomycin- and other antibiotic-sensitized ion-sensing bilayer properties of interest. A stabilizing medium compatible with electrical sensitivity and excitability was not found. A study of an alternative preparative approach was begun whereby a lipid monolayer was cast on a sheet of polyacrylamide hydrogel for making a lipid-centered sandwich of two such coated sheets. A bilayer supported by the surface of polyacrylamide-glycerol gel is unstable because the gel swells when immersed in water. It does not form a flat surface across a membrane-bearing hole, but swells and bulges through the hole, interfering with the formation of lipid bilayers on the hole. This dimensional instability could not be eliminated. The contract terminated September 25, 1971.

GENERAL ELECTRIC COMPANY, Schenectady, New York
Contract Amount: $79,706 Contract No: NIH-69-2238
DEVELOPMENT OF METHODS TO DETECT INCIPIENT FAILURE IN DEVICES
(P. Griffen, p.i.)

During this contract year, work has been concentrated in two areas: (1) chronic implantation of a Thermo Electron Corp. Model VII Left Ventricular Pump for diagnostic purposes has been carried out, and (2) investigation of the acoustic diagnosis of atherosclerosis has been underway. A TECO VII pump provided with a set of sensors capable of monitoring all phases of device dynamics was implanted in a calf and monitored for 47 days. By comparing the acoustic signature detected from sensors within the device with the signature obtained from a sensor on the chest wall it was established that a precordial pressure transducer is capable of sensing all significant acoustic information emanating from the TECO VII pump operating in situ. Analysis of data from accelerometers implanted with the device showed that operating dynamics of the implanted device are not significantly different from those obtained previously during an acute implant. It can be inferred, therefore, that the defect discriminants resulting from the acute study will also be valid in the chronic case. Results also indicate that acoustic monitoring of tissue growth on the pumping sac is apparently not likely to be successful.

The techniques developed for studying incipient failure in devices were extended to monitoring the state of the cardiovascular system. Monitoring of developing atherosclerotic lesions is based on the hypothesis that the changes in the arterial wall and those imparted to the flowing blood stream by a plaque will alter the acoustic signature generated in a characteristic fashion. In vivo experiments have indicated that a stiff wire calibrated drawstring apparatus may be used to introduce a known degree of radially symmetric arterial occlusion to the abdominal aorta of swine. This animal preparation will be used to investigate the acoustic effects of this occlusion. This acoustic information will be backed with intra-arterial high frequency pressure and point flow measurements in the vicinity of the restriction. This study is viewed as the initial step in developing acoustic discriminants for characterizing the effects of developing atherosclerotic lesions.

Complementing these in vivo studies a program of in vitro experiments is being carried out to investigate the relationships between the acoustic signal, the constriction geometry, and the resulting blood flow pattern under controlled conditions in which the geometries and flow parameters may be accurately determined and varied at will. The main emphasis in the upcoming contract year is expected to be further development of this acoustic technique for monitoring developing arteriosclerotic lesions in the cardiovascular tree.

GEOMET, INC., Rockville, Maryland
Contract Amount: $39,617 Contract Number: NIH-71-2429
IDENTIFICATION OF SERUM ENZYME LEVEL DETERMINATION TECHNIQUES
(Rudolph H. Moyer, p.i.)
The major emphasis of the program was on optimization of the Geomet Cassettes for screening creatine phosphokinase (CPK) levels in whole blood. A survey of oxidation-reduction indicators showed resazurin, which changes from blue to red on reduction, to be the most satisfactory of those tested for use in the CPK system. The performance of cassettes prepared with this indicator, when tested with blood, plasma and serum samples from a hospital laboratory, showed good agreement between cassette designations and assay values. Storage stability tests showed that cassettes held under ambient conditions in the envelopes normally used for packaging had a shelf-life of approximately 16 weeks. Comparable samples which were refrigerated or frozen showed no deterioriation after 24 weeks of storage. Initial studies indicated that preparation of cassettes in a format similar to that of CPK should be feasible for the enzymes, lactate deyhydrogenase (LDH), Alpha-hydroxybutyrate dehydrogenase (HBD) and glyceraldehyde-3-phosphate dehydrogenase (GAPD). Work in these areas will continue during the next year.

INTERNATIONAL TECHNICAL INDUSTRIES, Santa Cruz, California
Contract Amount: No additional funds Contract Number: NIH-69-2240
AN INEXPENSIVE MINIATURE PRESSURE TRANSDUCER
(W. Kaufman, p.i.)
Little additional work was carried out under the extension of this contract, while problems associated with prototype miniature pressure transducers were being evaluated. Transducers produced under this program were characterized by large non-systematic variations in transducer calibration, non-linearity, and hysteresis. Inability to produce usable transducers based on the original design concept was attributed to basic incompatibility between the ferrite and organic encapsulation materials in terms of structural integrity under mechanical and thermal stress and to lack of electrical integrity under stress because of inferior fabrication methods. This contract was terminated on April 9, 1972.

KONGISBERG INSTRUMENT, Pasadena, California
Contract Amount: $19,548 Contract Number: NIH-69-2241
TRANSDUCER IMPROVEMENT PROGRAM
(Eph Konigsberg, p.i.)
Development of improved pressure transducers has continued with the objective of improving baseline stability as a function of time. Emphasis has been placed on mechanical redesign with a redistribution of structural stiffness ratios (including a stiffer diaphragm) and tight tolerances on parts fabrication. Considerable progress was made in understanding the behavior of epoxy materials in the transducers and the contributions of these materials to instability. The total amount of epoxy adhesive in each transducer has been reduced, and suitable methods for preparation and processing of epoxies have been defined. Long-time precision monitoring of the calibrations of trans-

ducers has been continued as a means of evaluating the influence of fabrication methods and design changes on stability. Marked improvement in stability of P22 type transducers has resulted. Production of deliverable transducers has been held in abeyance subject to the completion of detailed improvements in the prototype designs. Future plans include fabrication and testing of deliverable transducers, development of an implantable differential pressure transducer, and study of stability and aging in sealed transducers.

WERNER P. SCHULZ, San Bruno, California
Contract Amount: $11,492 Contract Number: NIH-71-2043
DEVELOPMENT TECHNIQUES FOR PRODUCTION OF PRESSURE TRANSDUCERS
(Werner P. Schulz, p.i.)
This program is aimed at fabrication of improved, miniature, catheter tip capacitor pressure transducers of a type originally developed in a metallic design by NASA Ames Research Laboratories and subsequently by Smith Kline Instruments, Inc. (formerly Corbin-Farnsworth, Inc.). The transducer is mounted at the end of a catheter cable which has been changed to a coaxial design to replace the former triaxial cable used. The catheter diameter has been reduced to French 5 (1.67mm), and miniature connectors of comparable size are now employed. Extensive circuit optimization has resulted in a circuit design of high stability that eliminates signal variations caused by cable flexure and vibration. Fabrication of the transducer by microminiature glass techniques has resulted in a greatly simplified design involving basically only two parts: a hollow glass-to-Kovar feed-through type element fitted onto the catheter tip and a thin, circular, pressure-sensitive glass diaphragm sealed to it at the edge by a glass frit. The inner element and the outer diaphragm are metallized with gold to make conducting electrodes. The transducer is designed to have a frequency response exceeding 1 KHZ and to be sensitive to pressures as small as 0.1 mmHg (full scale 300 mmHg). The hand-crafted transducer fabrication has had numerous problems involving mechanical and electrical integrity following heat-sealing, microminiature parts handling, and quality control. Microscopic instrumentation techniques including optical polarization have been employed for inspection and quality control of the fine parts. If prototypes can be produced successfully, the design is suitable for mass production by automated methods at very low unit cost and greatly improved quality control. This fabrication contract will terminate at the end of the present contract period, on July 5, 1972.

WESTINGHOUSE ELECTRIC CORPORATION, Pittsburgh, Pennsylvania
Contract Amount: $91,587 Contract Number: PH43-68-661
DEVELOPMENT OF A CONTINUOUS PO_2/PCO_2 MEASURING SYSTEM
(P. Reichner, p.i.)
An instrument for the continuous measurement of PO_2 has been designed and tested in vivo. The system uses a solid electrolyte oxygen cell to measure the PO_2 in a small volume of gas which circulates through the external console and the intravascular catheter. Within the catheter, the gas is separated from the blood by an oxygen-permeable membrane. At equilibrium the oxygen tension in the gas is equal to that in the blood. In the non-null case,

the dPO_2/dt is directly related in the null PO_2. The instrument has been demonstrated to have satisfactory accuracy and a response time of less than 2 min. Capacity for the continuous measurement of PCO_2 is being added to the instrument. Severinghous and thermal CO_2 dissociation methods are being explored, the former having already been demonstrated in preliminary in vivo experiments. Eight PO_2 units capable of being adapted to include future PCO_2 capability, plus a pool of 50 catheters, are being fabricated and will be submitted for Test and Evaluation during FY 1973.

BIO-MATERIALS

During the past year, the emphasis on the practical aspects of materials development has continued. Among the most significant advances was the further development of the covalent bonding of micron-thin neutral hydrogels (polyhydroxyethylmethacrylate and polyacrylamide) onto a variety of polymeric substrates by both plasma discharge grafting and chemical grafting techniques. Largely due to this stimulus, other Institutes within the NIH are supporting successful work with hydrogels, and other investigators have also succeeded in demonstrating the potential usefulness of this class of materials in biomedical applications. In the heparinization area, the improved one-step method has been further advanced. In an attempt to diminish the heparin elution problem which is especially evident in certain high blood flow regions (arterial-venous shunts in sheep), the hydroxyl groups of heparin have been crosslinked with glutaraldehyde based on previous work in Sweden. *In vitro* and *in vivo* evaluations are in progress. To extend the usefulness of pyrolitic carbons to flexible structures, a vapor phase deposition technique has been further developed which permits the coating of various polymeric substrates, including microfibers, with pyrolitic carbons. Biological evaluations are in progress to compare the properties of these materials with LTI"Pyrolite" carbons. The development of block copolyether-urethanes continued to yield encouraging biological results both *in vitro* and *in vivo*. Likewise excellent preliminary *in vivo* performance in dogs was demonstrated for sulfonated copolystyrenes having a controlled degree of sulfonation. These materials might be useful for biocompatible, non-leachable coatings.

During the past year other contractors of the MDAP have concentrated their efforts on providing surfaces which can simulate the characteristics of the intimal lining of the human cardiovascular system. This involves the formation of a contiguous lining of cells which are nonthrombogenic, tightly adherent to the wall lining of a flexible surface, self-replicating and immunologically unrecognizable to the host's own tissues. The substrates are ultrathin nonwoven fabrics, consisting of polypropylene or nylon microfibers, which are used to coat the blood contacting surfaces of circulatory devices. Such materials are infiltrated by intimal cells and anchor the living lining of healthy tissue which then develops. Because these materials are extremely thin (<50 microns) and because the diameter of the fibers is extremely small (~1 micron), this substrate for tissue growth will permit development of an intimal lining which is thin enough to be adequately nourished by blood flowing over its surface. As a result, problems of tissue capsule degeneration should be minimized and may be eliminated entirely. Preliminary *in vitro* and *in vivo* studies in these areas have been extremely encouraging, and thorough quantitative and objective assessments will be available in the near future.

During the past year efforts of materials evaluations have been largely limited to the *in vivo* evaluation of candidate materials in arterial and venous blood, including the study of formation of renal emboli. A number of new materials are now able to pass these *in vivo* screening tests with little or no evidence of biological damage, within the limits of detection afforded by these short-term tests.

Future efforts will increasingly emphasize (1) the understanding of the interactions between blood and materials which is a necessary requirement for the development of long-term biocompatible materials, and (2) the development of improved techniques for the biological evaluation of materials for long-term uses.

ABCOR, INC., Cambridge, Massachusetts
Contract Amount: $73,594 Contract Number: NIH-71-2047
MICROFABRIC SUBSTRATE DEVELOPMENT
(Elie S. Nuwayser, p.i.)

The principal objective of this work is to develop microfiber surfaces on impermeable walls for use in cell culture and intimal lining development for implantable artificial heart devices. In this manner, the microfiber lattice will act as a scaffolding for anchoring a 50 mm layer of viable cells which receives its nutrition from the blood stream. To achieve such a sheer layer of microfiber restricts the diameter of the individual filaments to a few microns. Since filaments with diameters in this range are not available, a complex facility was built for continuous fabrication of microfiber nonwoven fabrics from thermoplastic polymers by hot melt extrusion. This facility is unique in its ability to produce microfibers with submicron diameters and produce a nonwoven mat in one step. The facility has been successfully used to prepare nonwoven nylon fabrics with filament diameters averaging one micron. Some filaments are as fine as 200 millimicrons. Using these fabrics a process was developed for lining Estane^{R} Polyurethane with a very sheer layer of microfabric for use in tissue culture and intimal lining development. This process was applied to the development of seamless linings for complex vascular devices such as tubes and heart pump bladders. Procedures and equipment were assembled for testing and characterizing the properties of the microfabrics. The properties of the microfabrics were measured and correlated with the operating parameters of the extruder. Future work includes preparation of nonwoven Dacron fabrics and the development of techniques to coat the inner surfaces of complex cardiovascular assist devices with the non-woven fabrics.

BATTELLE MEMORIAL INSTITUTE, Columbus, Ohio
Contract Amount: $41,958 Contract Number: PH43-68-649
STUDIES ON THE DEVELOPMENT OF MATERIALS FOR USE IN ARTIFICIAL HEART DEVICES
(Richard D. Falb, p.i.)

The further development of a simple one-step ionic heparinization process enabled the heparinization of various polymers besides silicone elastomers. This process involves the exposure of a material at ambient temperatures to an organic solvent containing a coupling agent such as tridodecylmethylammonium chloride/heparin (TDMAC/heparin) complex. While TDMAC/heparin treatment of silicone rubber showed excellent thromboresistance in many applications, when such heparinized arterial-venous shunts were implanted in sheep from the carotid artery to the jugular vein, only about 20 to 35 percent of the heparin complex remained after one week due to the elution of heparin in this high blood flow region. In an attempt to overcome this problem and on the basis of recent work by Swedish workers, Battelle has

been experimenting with glutaraldehyde to crosslink the hydroxyl groups of heparin and thus to stabilize the heparin complex. In vitro and in vivo evaluations are in progress. Further efforts will also be made to covalently bond heparin on to appropriate substrate materials and to prepare specimens for biological evaluations.

BATTELLE MEMORIAL INSTITUTE, Columbus, Ohio
Contract Amount: $148,134 Contract Number: NIH-71-2058
DEVELOPMENT OF INTIMAL LININGS
(J. B. Boatman, p.i.)
The main objectives of this contract are: (1) the development of methodologies for cell coverage of microfabrics as double-layered coatings, specifically of endothelial cells over fibroblasts; (2) the evaluation of new improved microfabric linings and their modification; and (3) the in vivo evaluation of microfabric surfaces. A variety of primary cell cultures have been prepared from tissues of the adult sheep and calf such as muscle, aortic and venous intima, and peritoneum lining. These cells have been seeded onto the microfabrics by gravity sedimentation and by a unit which can be rotated at variable speeds about two perpendicular axes. Some significant results are: (1) the in vitro demonstration of the nonthrombogenicity of endothelial cells on microfabrics, with the specific absence of platelet adherence or activation on their surface; (2) the in vitro demonstration of the culturing of double layers of both endothelial cells and fibroblasts to full sheeting over microfabrics; and (3) the prior cell coating of microfiber surfaces is accompanied by increased pseudointimal development and the increased adherence is paralleled by reduced renal infarction. Future work involves the in vitro and long-term in vivo evaluation of the growth and survival of pseudointimal linings on microfabric-lined devices and evaluation of layering pattern, penetration, and growth of mixed cell suspensions (minced blood vessels and peritoneal strips) on microfabrics.

CARNEGIE-MELLON UNIVERSITY, Pittsburgh, Pennsylvania
Contract Amount: $59,291 Contract Number: PH43-66-977
STUDIES RELATIVE TO MATERIALS SUITABLE FOR USE IN ARTIFICIAL HEARTS
(Robert L. Merker, p.i.)
Work continued on further improvement of the APTES (γ-aminopropyltriethoxysilane) method for the heparinization of thin (2 to 3 mils) silicone rubber and development of techniques for producing thin, pinhole-free silicone membranes. It has been shown that the permeability of thin silicone membranes to O_2 and CO_2 is virtually unaffected by APTES heparinization. Although the use of swelling agents in conjunction with the APTES heparinization method gave good results with small pieces of thin silicone membranes, larger pieces exhibited some physical deformations. Use of a swelling agent therefore was eliminated. Preliminary chemical tests have substantiated the expectation that sufficient heparin can be attached by the APTES method with thin membranes. Biological evaluation is in progress. Future work will include the development of interpenetrating polymer networks, using hydrophilic polymers with silicone rubber (so-called "snake-cage" polymers) and the investigation of these structures with respect to tensile properties, equilibrium water uptake, swellability, wettability, and blood clotting behavior.

DOW CORNING CORPORATION, Midland, Michigan
Contract Amount: $21,054 Contract Number: PH-43-66-979
DEVELOPMENT OF BLOOD COMPATIBLE SILICONE ELASTOMERS
(Jack L. Boone, p.i.)

The effort has been largely directed towards producing fabricated items from polyfluorosiloxane homopolymers and mixtures of this homopolymer with polydimethylsiloxane, both of which have been fully characterized in earlier years under this contract. Attention has been largely directed at potential blood oxygenation applications. A significant accomplishment was the adaptation of the polyfluorosiloxane (X-95538) to a dispersion system. This was a necessary first step in using this material to produce thin cast membranes for possible application in oxygenators. While some progress has been made in this effort, the fabrication of completely pinhole-free polyfluorosiloxanes at thicknesses of less than 5 mil was not achieved due to the inherent physical characteristics of the polymer. Non-supported, pinhole-free calendered films had been produced from the polyfluorosiloxane homopolymer (X-95538) and a 65/35 mole % mixture of this polymer with polydimethylsiloxane (X-95539) in thicknesses of 5 mils. The feasibility of producing small hollow fiber extrusions (O.D.=0.018", I.D.=0.009") for oxygenator applications from a 38/62 mole % mixture of polyfluorosiloxane and polydimethylsiloxane was demonstrated. The use of as little as 2% polydimethylsiloxane with the polyfluorosiloxane overcomes the "stickiness" of the latter, permitting extrusions. Due to the use of another polymer ±poly(carbonate-co-dimethylsiloxane)1 and also due to various proprietary considerations with the Dow Corning materials, this contract was terminated on February 29, 1972.

FRANKLIN INSTITUTE RESEARCH LABORATORIES, Philadelphia, Pennsylvania
Contract Amount: $28,998 Contract Number: NIH-71-2017
ACTIVE VAPOR GRAFTING OF HYDROGELS IN MEDICAL PROSTHESES
(Harvey Scott and Paul L. Kronick, p.i.)

The objective of this project is to fabricate blood compatible hydrogel-graft-coated cardiac and pulmonary assist devices, using atomized gas plasma grafting techniques. This process eliminates the inherent physical weakness of non-grafted hydrogels. The main effort focused on the use of block copolyether-urethane substrates and intra-aortic balloons made from these polymers. These were reproducibly graft-coated with the neutral hydrogel of polymerized 2-hydroxyethylmethacrylate. The presence of hydrogel coatings was confirmed by dyes, superior water wetting of the substrates, infrared reflection spectroscopy, and an increased water content of the graft-coated versus uncoated materials. It is estimated that the thickness of the hydrogel coatings is in the range of about two to four microns. A number of other polymeric substrates have also been successfully coated with 2-hydroxyethylmethacrylate. Future efforts will also utilize acrylamide hydrogel in view of the expectations that this material can take up even greater quantities of water than hydrogels based on 2-hydroxyethylmethacrylate. Previous in vitro and in vivo biological evaluations on non-grafted polyacrylamide hydrogels showed excellent blood compatibility. Similar biological evaluations are in progress with grafted hydrogel materials and the initial results are encouraging but as yet incomplete.

GULF ENERGY & ENVIRONMENTAL SYSTEMS, INC.
Contract Amount: $39,921 Contract Number: PH43-67-1411
COMPATIBILITY OF CARBON WITH BLOOD
(Donald Snowden, p.i.)
It has been shown in studies over the past several years that certain quasi-crystalline structures of elemental carbon have many chemical and physical properties necessary for medical devices. It has been demonstrated that LTI (low temperature isotropic) carbons are especially well-suited for such applications. However, these carbons are not suitable for applications requiring flexible or extremely thin structures. Vacuum vapor deposition provides a technique for preparing suitable thin carbon coatings with adequate flexibility. Work on the present contract has shown that some of the carbon coatings deposited on various polymers, including polymeric microfibers, have good adherence and mechanical integrity. Among the polymers investigated for coatings were block copolyether-urethanes, polyamides, a polyimide ("Kapton"), silicone rubber, and cellulose acetate. Encouraging results have been obtained on all but silicone rubber. Since these carbons are not identical to LTI carbons, thorough in vitro and in vivo biological evaluations are in progress. Future work will include the further investigations of the vacuum vapor deposition process, studies of adhesion of the carbon coatings on various substrate polymers, and the carbon coatings of various specimens, including microfibers.

JOHNS HOPKINS UNIVERSITY, Baltimore, Maryland
Contract Amount: $49,992 Contract Number: PH43-68-84
IN VIVO SCREENING OF POTENTIAL THROMBORESISTANT MATERIALS
(Vincent L. Gott, p.i.)
For the past four years new materials from materials research groups under contract to the MDAP have been evaluated in vivo. The materials have been fabricated into the shape of standard inferior vena cava test rings for acute and chronic implantation into the canine vena cava. In the acute test the rings are evaluated for a period of two hours. Materials demonstrating significant thromboresistance in this test are then further evaluated for a two-week period. Rings also have been used to study the effect of various methods of sterilization on the thromboresistance of the various biomedical materials. Evaluation has also been made of the effects of new surfaces when applied to a variety of substrates. A subcontract with the Cornell Aeronautical Laboratories, Inc. has provided surface chemistry tests, including MAIR infrared spectroscopy and Zisman contact angle studies, on a number of rings prior to and following two-hour caval implantation. These studies have been highly valuable in characterizing the outermost surface of these rings prior to implantation, and also in characterizing the nature of the deposit after a two-hour implant. During the past twelve months of this contract, new biomaterials developed by 16 different contractors of the Medical Devices Applications Program have been evaluated in a standard in vivo screen test. Materials that were evaluated and appeared to show significant or very encouraging thromboresistance results at this time include: 1) sulfonated polystyrenes; 2) plain hydrogel surfaces; 3) ionically and covalent bonded heparinized surfaces; 4) fluorosilicone elastomers; 5) highly polished

isotropic "Pyrolite" carbons; 6) epoxy polymers with added Pluronic surfactant; 7) polyurethane copolymer; 8) electrified polymer rings (electrets); 9) polyamino acid-polysiloxane block copolymer; and 10) vinyl acetate/crotonic acid copolymers. Surface chemical studies carried out by Cornell Aeronautical Laboratory, Inc. on these biomaterials before and after implantation have provided significant additional information regarding the nature of the thromboresistance of some of these materials. This contract has provided an acceptable screening mechanism for the materials program, and it is planned to continue this work during the next year.

LEE PHARMACEUTICALS, INC., South El Monte, California
No additional funds Contract Number: PH43-68-1409
DEVELOP IMPROVED ENCAPSULATION MATERIALS FOR IMPLANTATION
(Henry Lee, Jr., p.i.)
This contract was originally carried out by Epoxylite Corporation, a parent company of Lee Pharmaceuticals. During the first two years of the contract, a series of polyurethane and epoxy resin materials were developed for the insulation of implantable devices of interest to the Program Office. Several components and devices were encapsulated and subsequently implanted in test animals. During the current contract year, one of the encapsulation materials was reformulated due to the discontinuation of a source of supply of one of the ingredients. This reformulated polymer was satisfactory. In view of the stated lack of need for the encapsulation services of Lee Pharmaceuticals, this contract was terminated, on March 24, 1972.

LEE PHARMACEUTICALS, INC., South El Monte, California
Contract Amount: $27,516 Contract Number: PH43-68-1379
DEVELOPMENT OF IMPROVED MATERIALS FOR ARTIFICIAL HEARTS AND BLOOD OXYGENATORS
(Henry Lee, Jr., p.i.)
The aim of this project has been to duplicate some of the chemical composition of normal endothelium in a blood-contacting surface. The blood-exposed surface of normal blood vessels contains chemically attached N-acetylneuraminic acid which carries a negative potential and which is supported and insulated by a non-polar hydrocarbon layer made up largely of cholesterol, lipids, and fatty acids. This project utilized sialic acid and/or cholesterol as the blood-contacting layer. Model studies have indicated that cholesterol and/or sialic acid may be incorporated into polymeric chains by polymerizing monomers which already contain these materials as side-chains. Films and tubes of poly (vinyl alcohol) were prepared and coated with a variety of cholesterol and sialic acid half esters. These were examined by scanning electron microscopy and by infrared absorption spectroscopy. Model compounds containing bromine were prepared, and a surface attachment of molecules was demonstrated by neutron activation analysis. Initial two-hour vena cava ring tests in dogs showed very promising results with sialic acid-containing rings. Chronic (two week) tests are in progress. This contract was renewed for only six months. The work will include the further development, optimization, and characterization of an "artificial endothelium", blood-contacting layer which is composed of sialic acid and/or cholesterol. Also, greater emphasis will be placed on the

preparation of specimens for thorough in vitro and in vivo evaluation by other contractors.

POLYSCIENCES, INC., Warrington, Pennsylvania
Contract Amount: $56,761 Contract Number: PH43-66-1124
POLYMER STUDIES RELATED TO PROSTHETIC CARDIAC MATERIALS WHICH ARE NON-CLOTTING AT A BLOOD INTERFACE
(B. David Halpern, p.i.)
This project is aimed at the chemical grafting of polyacrylamide hydrogels onto block copolyether-urethanes and other suitable polymers in order to overcome the inherent mechanical weakness of non-grafted hydrogels. This work has been successful inasmuch as it is now possible to graft-coat block copolyether-urethanes routinely and reproducibly with polyacrylamide hydrogels in the micron thickness range. Very recently, preliminary experiments indicate that poly(carbonate-co-dimethylsiloxane), which is currently used in the hollow fiber oxygenators, can also be grafted with polyacrylamide hydrogels. Further development work is needed before the method can be routinely applied to coat the inside of hollow fibers. It is strongly suggested by the experimental data that highly purified non-ionic polyacrylamide hydrogels are as biocompatible as weakly anionic polyacrylamide hydrogels which have been copolymerized with weakly basic monomers. The biocompatibility of non-ionic polyacrylamide hydrogels is, however, diminished if proper purification is not used. This contract was renewed for only six months. The work will include the physical characterization of hydrogel-grafted surfaces, the further development of the chemical hydrogel grafting process, the investigation of the feasibility of grafting hydrogel to other polymeric surfaces, and the preparation of additional specimens for biological evaluations.

PROVIDENCE HOSPITAL, Seattle, Washington
Contract Amount: $103,280 Contract Number: NIH-71-2060
DEVELOPMENT OF INTIMAL LININGS
(Peter B. Mansfield, p.i.)
The main objectives of this contract are: (1) development of techniques for autologous and allogenic cell linings of prostheses; (2) development of techniques for applying cells to the microfabric devices without subsequent in vitro culturing of the devices; and (3) studies of factors influencing cell lining thickness. The ultimate goal of this work is to develop the practical capability of generating a biologically satisfactory blood/artificial conduit interface. During the past 12 months of the contract the utilization of bovine fibroblasts as tissue cultured cell linings for vascular prostheses has been evaluated. Techniques for cell culture and prosthesis seeding have been developed and standardized. The effectiveness of artificial surfaces as a support for the growing of cells has been evaluated with regard to rate of cell growth, uniformity of covering, cellular penetration and cell adherence to the fabric. An in vitro shear testing device has been developed to evaluate cellular adherence. Results show that the shear force generated conforms to theory. Shear disruption of cell-prosthesis attachment varies with fabric type and surface configuration. Techniques for the surgical implantation of

tubes lined with fiber surfaces have been developed and standardized. The effect of heparin on the coagulation sequence has been studied in calves. Present and future work involves: (1) the development of techniques to isolate true endothelial cell lines; (2) the study of the characteristics of early in vivo fibrin deposition; (3) the evaluation of altered blood coagulation on fibrin deposition to implanted prosthetic material; (4) the evaluation of cellular intimal lining surface activity and fibrin deposition; and (5) the in vivo evaluation of new cardiovascular materials and microfabric lined devices with and without tissue culture coverings.

STANFORD RESEARCH INSTITUTE, Menlo Park, California
Contract Amount: $80,212 Contract Number: PH43-64-84
DEVELOPMENT OF MATERIALS FOR HEART ASSIST DEVICES
(John L. Brash, p.i.)
The project effort has been directed to the development of block polyether-urethane elastomers for use in the fabrication of intra-aortic balloons, blood pump diaphragms, and other heart assist devices. The overall biocompatibility of these polyurethanes is very encouraging as judged from in vitro and in vivo biological evaluations. In addition, work has been initiated on the synthesis of sulfonated polymers that might be useful as blood compatible coatings. Recent in vivo results (vena cava and renal embolus) indicate very encouraging results with this type of polymer. A patent application has been filed with the U. S. Patent Office in the name of John L. Brash (Stanford Research Institute) and Stephen D. Bruck (National Heart and Lung Institute) describing the two-stage wax mandrel solution casting process which is currently being used by Tecna Corporation under contract to the MDAP/NHLI. It was found that the use of waxes that are chemically pure and insoluble in dimethylformamide and are free of low molecular weight leachable impurities will maintain the good biocompatibility of the polyether-urethane used in the fabrication of intra-aortic balloons. Future work will include the continued development of block copolyether-urethane elastomers with specific mechanical properties and optimum blood compatibility, the supply of intermediate-size quantities of block copolyether-urethanes, continued investigation of castable polyurethanes, hydrophilic polyether-urethanes, and sulfonated polystyrenes.

STATE UNIVERSITY OF NEW YORK, DOWNSTATE MEDICAL CENTER, Brooklyn, N.Y.
Contract Amount: $27,842 Contract Number: PH43-68-75
NEW APPROACHES IN THE SELECTION OF MATERIALS COMPATIBLE WITH BLOOD
(Philip N. Sawyer and Supramaniam Srinivasan, p.i.)
Adsorption and electron transfer reactions of blood proteins (fibrinogen, Factor V and Factor VIII) have been investigated using potentiostatic and potentiodynamic methods. Individual purified blood coagulation proteins (in saline) were used. The three proteins undergo electron transfer reactions at the metal (platinum)-solution interface. The charge transfer peaks are influenced by adsorption in all cases. Fibrinogen takes part in both anodic and cathodic charge transfer reactions. Factor V is adsorbed on the Pt surface over a wide range of potential (-600 to +900 mv vs S.C.E.) and takes part in a cathodic reaction. Factor VIII is involved

in a few charge transfer reactions as revealed by potential sweep studies. It is probable that the large number of peaks observed for Factor VIII is due to adsorption of reactants and/or products. Future work involves the potentiostatic measurements of the crude and purified fibrinogens in Krebs solution and in NaCl over the potentional range -800 to +1000 mv. The cathodic potential region will be studied in greater detail. Spectrophotometric analysis of fibrinogen content and clotting time studies will be carried out.

THERMO ELECTRON CORPORATION, Waltham, Massachusetts
Contract Amount: $18,220 Contract Number: PH43-66-1126
DEVELOPMENT OF ELECTRIFIED POLYMERS FOR USE IN CARDIAC ASSIST DEVICES
(Preston V. Murphy, p.i.)
The current phase of this investigation involves the further development of electrification techniques to enable the polarization of the blood contacting surfaces of selected medical devices, and the preparation of specimens for in vivo biological evaluations. Several components and devices were coated with carnauba wax and then charged triboelectrically to yield negatively-charged surfaces. This effort included a polypropylene leaflet valve and a polypropylene tricuspid valve. Attempts to fabricate vena cava rings of Celcon coated with Nichols NE-F350 polyurethane were not successful; however the use of Kel-F as the substrate appeared to be satisfactory. Work is in progress to impregnate the Nichols NE-F350 polyurethane coatings with carnauba wax and charge it triboelectrically to induce a negative polarization of the surface. Work has also been carried out on pump bladders for the left ventricular assist device, Model #7. A complete bladder made of Nichols NE-F350 polyurethane was coated with carnauba wax and charged triboelectrically. Subsequent flexing of the pump bladder under simulated conditions in a mock loop and contact angle measurements suggested good stability of the surface electrification. Future work, subject to contract renewal, might include the characterization of electrically-polarized surfaces and the better understanding of the role of such surfaces in blood compatibility.

UNION CARBIDE CORPORATION, Bound Brook, New Jersey
Contract Amount: $130,711 Contract Number: PH43-68-1388
FIBER SUBSTRATES FOR TISSUE CULTURE AND INTIMAL LINING DEVELOPMENT
(Joseph S. Byck, p.i.)
The specific objective of this research has been development of an extremely thin fabric-like material which can be bonded to the blood-contacting surfaces of circulatory assist devices. The purpose of this material is to provide a porous network which can be infiltrated by tissue cells and which will serve as a matrix for development and anchoring of a layer of healthy intimal tissue. This layer of tissue or "neointima" would serve as a blood compatible living lining for the device. Although work was initially undertaken on several approaches to development of blood compatible polymers, all efforts of this contract have now been concentrated on continued development of a single highly promising polymeric materials system. This is an ultrathin nonwoven fabric, consisting of polypropylene microfibers, which will be used to coat

the blood-contacting surfaces of circulatory assist devices. The materials system is prepared from immiscible polymer microfiber tapes produced by co-extrusion of polypropylene and an acrylic acid copolymer. After extraction of the acrylic component, the tape can be transversely drafted 100-150 fold to produce an ultrathin nonwoven fabric which acts as the tissue growth substrate. After bonding with pressure sensitive adhesive to nonporous polymeric or metallic substrates, the ultrathin fabric can be conformally coated with one micron or less of vapor deposited Parylene C. This polymeric coating serves both to reinforce the microfiber network and to provide a biologically compatible surface which will be atraumatic to cells. In addition, it has been demonstrated that the performance of Parylene C-coated microfibers in in vitro and in vivo experiments is significantly enhanced if they are made more hydrophilic by exposure to an appropriate electrical discharge. During the past year, significant progress was made in several areas which has led to initiation of an extensive program of in vivo testing in calves. One major problem had been regulation of the porosity of the microfiber webs to provide a structure which was sufficiently porous to be penetrated by cells and which could accommodate whole cells in voids beneath the surface of the web, but which exhibited sufficiently high fiber density to mechanically entrap the intimal lining formed by proliferation of these cells. A method for accomplishing this, known as "vertical drafting", was developed. Using this technique, fiber webs could be prepared containing large (20-40 micron) pores in a surface layer, while retaining closer fiber spacing in the strata beneath the surface. Repetition of the vertical drafting procedure was found to produce fiber networks with numerous 20-40 micron pores throughout or, if desired, could be used to produce openings in the network which are 100 or more microns across. Future work involves the development of new, more hydrophilic parylenes and the development of techniques to bond the nonwoven fabrics to the inner surfaces of complex devices.

UNION CARBIDE CORPORATION, Bound Brook, New Jersey
Contract Amount: $25,457 Contract Number: NIH-71-2067
INVESTIGATIONS OF POLYELECTROLYTES
(Joseph S. Byck, p.i.)

In order to produce polymers having improved blood compatibility, this investigation has largely focused on copolymer systems which are combinations of a carboxyl containing monomer (i.e., acrylic or crotonic acid) with a second monomer containing no ionizable moieties. To a lesser degree, sulfonic acid-containing polymers were also investigated. Two parameters, concentration of ionizable groups and degree of neutralization, were found to play significant roles in reactions with blood. An organized study was made to characterize the effects of these parameters. Effort was also directed toward the development of a series of hydrophilic polyelectrolytes. Of the polymer systems developed, poly(vinyl acetate-co-crotonic acid) was found to be most promising. This is a highly hydrophilic polymer that becomes water soluble when partially converted to its salt. However, it can be radiation-crosslinked to form insoluble, water-swellable polyelectrolyte hydrogel coatings. The poly(vinyl acetate-co-crotonic acid) that had been converted to 60% sodium ion monomer and containing approximately 2% crotonic acid, remained thrombus-free in vena

cava rings in dogs for up to two weeks. Future work will be aimed at the preparation and characterization of vinyl acetate/crotonic acid copolymers and ionomers, and N-vinyl pyrrolidone/acrylic acid copolymers and ionomers. Also efforts will be made to develop covalent bonding techniques for the attachment of the above polymers to appropriate polymeric substrates.

UNIVERSITY OF MICHIGAN, Ann Arbor, Michigan
Contract Amount: $46,023 Contract Number: NIH-71-2054
PRODUCTION OF MULTIPLE-LAYERED INTIMAL LININGS BY PERFUSION CULTURE
(Raymond H. Kahn, p.i.)

In an attempt to develop viable intimal linings for artificial vascular prostheses, an investigation of (a) potential cell sources, (b) methods to stimulate cell deposition and adherence to microfabric lined samples and (c) methods to stimulate cellular propagation were undertaken. Three cellular sources were investigated; namely, buffy coat, cells derived from bovine vessels and an established cell line WI-38. While buffy coat did not prove adaptable to surfaces, both the intimally derived cells and WI-38 were useful. The endothelial derived cells readily adapt to surfaces but yielded mixed populations which have resisted separation to date. The WI-38 has been singly successful in the development of seeding methods and for studies on proliferation. Technical procedures for seeding, adherence and growth developed during the period of this contract included (1) methods of degassing of the microfabrics prior to seeding to insure penetration of cells; (2) low centrifugation to forcibly seed cells into the microfabric; (3) containment of cells during the early stages of in vitro cultivation to prevent outgrowth of newly seeded cells; (4) perfusion of the cultures on a fixed schedule to permit constant removal of waste products and replacement of media. To date the studies have been primarily with Union Carbide fabrics. Of the fabrics tested, the non-vertically drafted, discharge-treated fabrics were decidedly better suited for cell attachment of the WI-38 cell when the technical procedures outlined above were utilized. On the other hand, multiple-drafted and maximally-drafted fabrics from Union Carbide were less effective in providing adequate surface for cell attachment. While the adhesive used in cementing the microfabric to a backing is undoubtedly toxic, the parylene C coating does an adequate job in protecting the cells. Present and future work involves the further characterization of the conditions necessary for complete seeding by the perfusion method, including (a) the number of cells required per unit of area, (b) optimal G forces necessary for seeding, (c) further study of required nutritive factors, including the rate of perfusion, and (d) the need to test devices for seeding three-dimensional objects by rotation along two perpendicular axes. Characterization of the cell-fabric inter-relationship by both light and electron microscopic procedures, utilizing ultrathin sectioned material is underway.

UNIVERSITY OF VERMONT, Burlington, Vermont
Contract Amount: $41,440 Contract Number: PH43-68-1427
THE EFFECTS OF MATERIALS ON BLOOD LEUKOCYTES, ERYTHROCYTES AND PLATELETS
(Bert K. Kusserow, p.i.)

The major objectives of this program are: 1) continued *in vivo* testing of candidate materials from other MDAP contractors using the standard renal embolus test system which has been developed and refined during past contract work; 2) further investigation of an *in vivo* blood-materials exposure system; 3) *in vivo* perfusions of eight-hour and sixteen-hour duration to assess the influence of surface and perfusion trauma upon blood corpuscles under *in vivo* circumstances; 4) development of a satisfactory method for determining the bacteriocidal capability of leukocytes; and 5) determination of platelet glucose metabolism. Nineteen test rings were implanted and evaluated in the renal embolus test system during the past year. Eleven rings were received from the Stanford Research Institute including three hydrophilic polyurethane, five copoly styrene/styrene sulfonate and three polyurethane rings. Also evaluated were four poly (hydroxyethyl methacrylate) hydrogel rings from the Franklin Research Institute and four acrylamide hydrogel rings from Polysciences. The thromboembolic patterns encountered during this implant series indicate that both the Stanford hydrophilic polyurethane and copoly styrene/styrene sulfonate possessed a noteworthy freedom from thrombotic deposits upon the ring implant surface proper. On the other hand, the presence of significant renal infarction in each of these implantation specimens suggested that antecedent ring thrombosis and detachment of thrombotic deposit from the very smooth walls of these implants had occurred to a certain extent in each of the implantations. The Stanford polyurethane 3-1000/425 (70/30)-1-X rings as well as the polyacrylamide hydrogel rings from Polysciences appear to display an intermediate degree of thromboresistance. The very frequent occurrence of renal infarcts suggested that rigid, non-pulsaing, smooth walled intravascular synthetic surfaces provide a very poor mooring surface for thrombotic deposits, a circumstance which in all probability predisposes to detachment and peripheral embolization. The poly(hydroxyethyl methacrylate) hydrogel rings from the Franklin Institute did not, under the circumstances of the renal embolus test system, display a noteworthy resistance to thrombosis. However, polyacrylamide-grafted hydrogels from Franklin Institute will be evaluated shortly. Other studies included the effects of perfusion and surface-induced blood trauma under circumstances of prolonged peripheral *in vivo* perfusions. The significant alterations in hematological parameters observed after eight hours of continuous *in vivo* perfusion are as follows. Significant elevations in total white blood cell count were observed in five perfusions. Mild decreases in total platelet count were observed in seven perfusions. A decrease in the phagocytic index of granulocytic leukocytes was noted in nine experiments. A significant rise in clot retraction index was also apparent throughout the series. Post perfusion differential white blood counts revealed increased numbers of band cells and decreased numbers of lymphocytes. Monocytes and eosinophils showed no noteworthy alterations, nor were significant changes observed in the level of circulating plasma serotonin. A series of similar *in vivo* perfusions of sixteen hours duration has also been completed, and the results are currently under analysis. A reasonably simple and satisfactory method was devised to determine the bacteriocidal capability of leukocytes obtained from samples of untraumatized blood and blood traumatized by *in vitro* pumping in the

standard pump circuit. Results have been consistent and reproducible in a large number of duplicate determinations. In preliminary tests (7 experiments) the bacteriocidal capability of pumped leukocytes appears higher than that of control leukocytes, while leukocytes obtained from blood which had been passively rotated in closed segments of pump tubing throughout the pumping period had assumed an intermediary position. These experiments are currently continuing.

MEDICAL DEVICE APPLICATION

Certain Medical Devices Applications Program contractors have served the development process primarily in the physiologic testing of the effects of prototype devices. Early in vivo testing of devices has been performed in several laboratories and has identified problems and produced information about device feasibility, efficacy, and anatomic and surgical constraints.

MDAP has established two Test and Evaluation Facilities where devices can be objectively tested and evaluated when development has reached a point at which clinical application can be considered. The basic objectives of the Test and Evaluation Program are: (1) to provide third-party evaluation for protection of the patient, the developer, and the Medical Devices Program from hazardous or ineffective medical devices; (2) to achieve expeditious general clinical application of newly developed devices which prove to be effective, reliable, and safe.

The test and evaluation process includes four phases: screening, pre-clinical in vivo and in vitro testing, initial clinical application, and broad clinical trial at satellite clinical facilities. A task force representing the scientific community is appointed for each device or class of devices to provide advice to the Heart and Lung Institute and information to the medical community during the T&E process. A large portion of the activity to date has been directed toward the development of facilities at the Illinois Institute of Technology Research Institute and at the University of Utah. Both these facilities are now operational. The staff associated with both facilities includes a multidisciplinary group of professionals with scientific, medical and engineering expertise.

BAYLOR UNIVERSITY COLLEGE OF MEDICINE, Houston, Texas
Contract Amount: No additional funds. Contract Number: PH43-67-1424
MECHANICAL PUMP DEVICES AND CARDIOVASCULAR CONTROL
(John H. Kennedy, p.i.)
This contract was for experimental studies (using a Hamilton Standard co-pulsator unit developed under contract number PH43-67-1112) aimed at the definition of baroreceptor, autonomic reflex loops, examining and comparing autonomic reflex alterations in response to "co-pulsation" and "diastolic augmentation" modes of circulatory assistance. Data was expected to provide insight into control parameters of circulatory assist devices. Results from the contract were not sufficient to warrant continuation and it terminated April 30, 1972.

ILLINOIS INSTITUTE OF TECHNOLOGY RESEARCH INSTITUTE (IITRI), Chicago, Illinois
Contract Amount: $1,745,917 Contract Number: NIH-69-2125
ESTABLISHMENT AND OPERATION OF A TEST AND EVALUATION FACILITY
(M. P. Kaye, p.i.)
The basic objectives of this contract during the current fiscal year included

continued facilities development and the test and evaluation of specific devices. The activities completed during the past year have significantly enhanced the operation of the T&E Facility. The development of software for the two tier XDS Sigma-3, Univac 1108 data acquisition and processing system has continued. Numerous software programs have been written to facilitate both data acquisition and data reduction. Over 300 calves were subjected to clinical procedures in the Facility. A record system has been developed which permits critical evaluation of the animal's course from time of entry into the Facility through post-mortem examination. Improvements in the biochemical and hematology laboratory have also been accomplished. The cardiac catheterization laboratory is nearing completion. The Facility concentrated on the test and evaluation of two devices, the Dow capillary membrane oxygenator and the intra-aortic balloon (IAB) system. The 1 L/min and 3 L/min Dow oxygenators were subjected to screening and preclinical in vivo and in vitro testing. On December 3, 1971, the Oxygenator Task Force recommended initial clinical trials. Clinical trials have been initiated. Preclinical in vivo and in vitro testing of the Westinghouse Model 4 and Model 5 IAB systems and the Tecna balloons have also been performed. Preclinical testing of commercial IAB systems are also being performed in conjunction with the overall IAB effort. Other efforts in process include the Geomet CPK cassette screening study, a prolonged bypass study with Dow units, and screening of the Tecna Organ Preservation System.

The planned FY '73 T&E effort includes: completion of Dow oxygenator clinical testing for prolonged bypass studies with the Dow units, completion of IAB activities, completion of screening and clinical evaluation of the Geomet CPK cassette, preclinical evaluation of the Tecna Organ Preservation System, preclinical and clinical evaluation of the Tecna respirator, membrane oxygenator studies, and the evaluation of an external sequential pulsation device.

MELOY LABORATORIES, INC., Springfield, Virginia
Contract Amount: $72,432 Contract Number: PH43-67-1418
PHYSIOLOGICAL EFFECTS OF BLOOD PUMPS IN ANIMALS
(B. Dennison, p.i.)

Meloy Laboratories has served the Medical Devices Applications Program as a facility for the in vivo testing of several devices developed by Program contractors. Prototype devices were brought to the facility by developers where they were preliminarily tested in the bovine or canine model. Early evaluation was made of feasibility and efficacy and solutions were found to surgical problems. During FY 1972 several different intra-aortic balloon materials were tested, the TECO veno-arterial bypass pump prototypes were tested, the Tecna respirator underwent initial functional evaluation, and a study was made of the optimum pumping parameters and acute cardiopathological effects of the Tecna mechanical ventricular assist device. The contract has been extended, without additional funds, to September 5, 1972.

TRAVENOL LABORATORIES, INC., Morton Grove, Illinois
Contract Amount: $286,391 Contract Number: PH43-67-1425
PHYSIOLOGIC EFFECTS OF CIRCULATORY ASSIST DEVICES
(F. Galysh, p.i.)
In past years, Travenol has evaluated the in vivo effects of several new devices for the Medical Devices Applications Program Office. During FY 1972, work focussed on implantation in calves of total artificial heart system components developed by several contractors under Program Office direction. Extensive studies of surgical implantation techniques, anatomic constraints, as well as function of blood pumps, control systems, power systems and related interfacing were carried out in more than 60 calves. The physiological effects of total heart system implantation were studied in another eleven animals which survived one to two days. Information obtained from these studies was valuable to contractors in conducting their iterative development efforts. This contract will continue to be directed toward evaluation of circulatory assist devices.

UNIVERSITY OF UTAH, Salt Lake City, Utah
Contract Amount: $1,559,000 Contract Number: NIH-70-2081
ESTABLISHMENT AND OPERATION OF A TEST AND EVALUATION FACILITY
(Reed Harker, p.i.)
The Utah contract was originally initiated in December 1969. The key objective initially included the planning and erection of a special purpose building. Completion of this building (50,000 sq. ft.) was accomplished in December 1971. A large portion of the FY '72 effort was directed toward facility development efforts. Software for the XDS Sigma-3 data acquisition and processing system has been developed and the system is operational. Numerous programs have been written to facilitate both data acquisition and data reduction. Considerable effort was directed toward each of the supporting laboratories. Installation of the cardiac catheterization laboratory was initiated but has not been completed to date. The T&E efforts during FY '72 included the Dow oxygenator screening study, initiation of Dow oxygenator clinical testing, preclinical evaluation of the Westinghouse Model 4 IAB system and Tecna balloons, screening of the TECO Veno-Arterial Bypass system (VAB) and preclinical testing of the TECO VAB. The projected FY '73 activities include the completion of the TECO VAB system preclinical testing, clinical testing of the TECO VAB system, clinical evaluation of the Geomet CPK cassettes, preclinical and clinical evaluation of the Tecna respirator, membrane oxygenator studies, and engineering testing of the sequenced external pulsation device. Facility development efforts will also be continued.

SPECIAL PROGRAMS

Artificial Heart Development

Two recent MDAP developments have significantly advanced the state-of-the-art of artificial hearts. The contracts involved in this development were: Aerojet Liquid Rocket Company (NIH-71-2488), ARCO Nuclear Company (NIH-NHLI-72-2900 [D]), McDonnell Douglas Astronautics Company (PH43-NHLI-67-1408), Stanford Research Institute (PH43-67-1422), Statham Instruments, Inc. (PH43-NHLI-68-1502), Thermo Electron Corporation (PH43-68-1455), and Travenol Laboratories, Inc. (PH43-67-1425). These developments were:

(a) The first atomic-powered heart engine has been implanted. A heart-assist system with the nuclear engine was implanted in a calf on February 14, 1972, to confirm procedures and acquire short-term data, thus initiating the evaluation in the living animal of a nuclear engine for powering the artificial heart or heart-assist; and

(b) The first total replacement artificial heart to be totally implanted has been developed and has undergone short-term animal tests. This implant is powered electrically, but may also be powered by a small implantable nuclear engine. The complete system is now ready for long-term animal trials.

Both the artificial heart and the heart-assist system are performing up to design specifications and yielding vital information for analysis by the scientists and engineers of the development team.

These two developments follow over four years of research and development on the nuclear engine for powering both kinds of artificial heart devices and two years of research and development on the total replacement artificial heart. With the development of the major components (pump, control and engine), the totally implantable total heart replacement can now be further studied for adaptation to human heart patients. These achievements, and the opportunities they afford for studying the biological and engineering problems involved in replacing the heart, may lead to a decision for developing the clinical systems for humans within a period of three and one-half to four years.

Heart-Assist System: The nuclear-powered heart-assist system implanted in a calf recently consists of two major units, one in the chest and the other in the abdomen.

In the abdomen is a six-pound, 3-by-8-inch cylinder containing a miniature thermal engine with a nuclear heat source. Hydraulic pressure generated by this engine is conveyed via tube to the blood pump and the control unit located within the chest.

The 50-watt heat-energy source is about 100 grams of Plutonium-238 (Pu-238) in a 3-layer metal capsule designed and proven to withstand corrosion, high impact and crush pressures, and cremation, as well as the maximum credible accident temperature of 2400°F. Pu-238 is primarily an emitter of alpha

particles, which have high energy but very low penetrating power and can be stopped by a thin piece of paper. The source also emits more penetrating gamma and neutron radiation, which are reduced to acceptable levels by capsule and engine design.

The heat from the isotope capsule is stored and released as required to power the thermal engine. Heat storage is achieved through the melting of a lithium salt material that has a high heat capacity and melts between 930 and 1200°F. The hot capsule and heat storage material are surrounded by an insulation jacket that directs the heat through the engine to produce useful power for operating the implanted blood pump.

Two nuclear thermal engines have been tested. One is a vapor cycle steam engine, the other a modified Stirling-cycle engine. These engines have undergone bench testing with the isotope and have entered animal testing phases with heart-assist pumps based on designs by Dr. Harmison.

The pump also features a blood-cooled heat exchanger that dissipates 70% or more of the excess heat from the engine, and a lining of flocked Dacron fibers to promote the growth of a blood-compatible layer of living tissue on all blood-contacting surfaces. Control logic mechanisms built into the unit enable the system to adjust and modify blood flow output, on a beat-by-beat basis, to conform to changing circulatory demands of the body.

About five years ago, at the time of the paper evaluation of artificial heart feasibility, many questions were flagged which could not be answered by available data. For example, no blood pump had been implanted for an extended period, the efficacy of such pumps was a matter of debate, the ability of the body to dissipate the reject heat and tolerate the requisite nuclear radiation was questionable, and no miniature thermal engine had achieved more than a tiny fraction of theoretical efficiency.

During the past five years, significant progress has been realized in these and other critical areas. Some of the more important milestones in establishing the feasibility of nuclear-fueled circulatory support systems include:

- Development of a blood-compatible pump interface;
- Seven months survival of a calf implanted with a functioning left ventricular assist pump;
- Assumption of total circulatory support of a calf (natural heart fibrillated) for two and a half weeks;
- Implantation of heat and radiation sources (16-and 24-watt Plutonium-238) well tolerated in dogs for over two years;
- Confirmation that heat loads up to 60 watts can be dissipated by animals;
- Demonstration in vivo of prototype circulatory assist systems (using both gas and vapor cycle thermal engines);

- Achievement of thermal engine efficiencies greater than 16 percent; and

- Demonstration of thermal engine life in excess of 5,000 hours (7 months).

Totally Implantable Artificial Heart: A totally implantable artificial heart, complete with power and controls, has been developed. This is the first complete unit to replace the heart and be self-contained within the body.

The artificial heart is similar to the natural heart, i.e., it contains four pumping chambers--two atria and two ventricles. The energy unit is nested between the blood-pumping chambers of the heart. The system consists of the pumping chambers, the energy converter, the heart-controlled computer and implanted energy storage and receiving units.

The feasibility of the complete system has been demonstrated in the engineering and acute animal phases of study; it is now entering the phase of long-term evaluation in animals.

Specific benefits accruing from the total replacement heart effort include:

- The application in animals of concepts for pumping and control of the total heart;

- The definition of surgical procedures and instrumentation technechiques for the application and evaluation of the totally implanted heart system;

- The acquisition of critical physical science and engineering data on each component and the functional aspects of the components in the intact animal;

- The determination of total heart pumping characteristics (including efficiency, filling characteristics, and responsiveness) required to satisfy physiologic needs; and

- The use of the totally implanted heart in animals to serve as a variable, controllable research tool.

There appear to be no major gaps in the data required to proceed to chronic animal testing.

ANNUAL REPORT OF MYOCARDIAL INFARCTION BRANCH

July 1, 1971 through June 30, 1972

BRANCH SUMMARY

The mission of the Myocardial Infarction Branch is to plan, implement and direct a program of research to reduce death or disability from myocardial infarction, chronic coronary heart disease and sudden cardiac death. Subdivisions of the program are presently focused on two of these three clinical areas, and upon physiological and biochemical processes fundamental to new therapeutic methods. Major objectives include improved detection and diagnosis, better understanding of disease mechanisms, and more effective prophylactic, acute and rehabilitative therapy.

In Sudden Cardiac Death, 19 contracts have been active in the past year. Their objectives are to develop methods for identifying sub-groups in the population chronically at high risk for sudden cardiac death, to develop the means of recognition of premonitory warning signs, to identify and characterize possible precipitating factors and patho-physiological processes, to characterize underlying chronic and acute pathology, to develop clinical-pathological correlations and to develop and assess means of early therapy of the suspected heart attack victim to prevent sudden cardiac death. To permit improved characterization of cardiovascular pathophysiology in the course of everyday activities, a request for proposals was distributed for equipment to record the electrocardiogram continuously and the blood pressure intermittently and automatically in ambulatory persons; the award of a contract is expected early in the coming fiscal year.

Under Acute Myocardial Infarction the major activity is the nine Myocardial Infarction Research Units. Their objectives are to conduct comprehensive clinical investigation on patients with acute myocardial infarction, to support relevant non-clinical and basic science investigations, and to develop some of the requisite tools and methods for the clinical research. Three other contracts are specifically directed at developing methods for quantifying infarct size suitable for repeated clinical use.

Under Physiological and Biochemical Processes Fundamental to New Therapeutic Methods, six contracts have been active upon the topic of Protecting Ischemic Myocardium and an expansion of this effort is imminent as a result of a further solicitation on this topic. These investigations are directed at elucidating the physiology and biochemistry of ischemic myocardium and at developing methods for protecting ischemic myocardium from progressing to irreversible damage. Since arrhythmias account for a substantial fraction of sudden and even of late cardiac deaths, and since preventive and therapeutic methods for their control are inadequate, a request for proposals on Control of Lethal Arrhythmias was distributed and the award of contracts is pending.

Significant advances have been made in the past year in the understanding of the hemodynamic, electrophysiologic, biochemical, and anatomic correlates and in the natural course of the disease. This information about the course of events leading up to sudden cardiac death, about the premonitory period of acute myocardial infarction, the acute in-hospital phase of the disease, and the post-hospital recovery phase, has been important in attempts to modify the pathological processes. Subgroups of patients within each phase of the disease have been identified in which prognosis, anatomy and pathophysiology are distinct. Pharmacological, surgical, and mechanical circulatory assist therapeutic interventions are being evaluated in specific subgroups of patients. New methods to measure hemodynamic chagnes, to assess the amount of infarcted and infarcting myocardium, and to quantify drug and hormonal levels in blood have been developed; they are in use clinically to evaluate therapy. Fundamental studies at the tissue cellular and subcellular levels have identified important underlying mechanisms in the myocardial cell which are altered under ischemic conditions and may be causally related to eventual myocardial cell injury and death.

SUDDEN CARDIAC DEATH

Sudden cardiac death or death prior to hospitalization accounts for over half of the 600,000 annual deaths from arteriosclerotic heart disease. A program of research on the onset of myocardial infarction and sudden cardiac death is being conducted to identify subgroups of the population at high risk for suffering one of these events, to develop better recognition of premonitory warning signs, to characterize underlying pathophysiological processes, and to develop and to assess means of therapy and patient care, both acutely for those with symptoms and chronically for those at highest risk. These objectives are being pursued in several ways - by epidemiological studies to define risk factors; by collaborative clinical-pathological correlations of sudden cardiac deaths using medical examiner's resources and interviews; by the correlation with prognosis and clinical events of the 24-hour electrocardiogram, exercise electrocardiograms, bifascicular block, sleep pattern and arrhythmias, coronary angiograms, and "unstable angina" treated medically or surgically; by the development of means of early therapy as in special ambulances and the acquisition of data early in the course of suspected myocardial infarction in these facilities, and by the assessment of the effects of intramuscular administration of atropine and lidocaine early in the face of suspected acute myocardial infarction.

In addition to previously recognized high risk factors for sudden cardiac death, which are generally similar to those for acute myocardial infarction, clinical-pathological correlations have shown an unexpectedly high incidence of sudden cardiac death in association with hypertensive heart disease and cardiomegaly; the incidence of sudden cardiac death in blacks is comparable to that in whites, in contrast to an apparent relatively low incidence of non-sudden death due to arteriosclerotic heart disease in blacks compared to whites. Ventricular arrhythmias observed in the course of 24-hour recordings in ambulatory persons and failure to develop "normal" elevations of heart rates during the course of the day correlate with a higher risk of sudden cardiac death as observed in long-term serial studies on several hundred middle aged men. Bifascicular block, particularly left bundle branch block, is also a risk factor, but manifests itself usually by the development of cardiac failure and death rather than by abrupt conduction disturbance. The follow-up on 100,000 middle-aged persons who had undergone routine multiphasic examinations has revealed 250 cases of sudden cardiac death and 450 cases of myocardial infarction; matched controls are being obtained from the group and analysis for numerous potential risk factors will be obtained in the coming year.

Premonitory symptoms of sudden cardiac death have been sought. Although as in previous studies approximately a quarter of patients have seen the physician two weeks prior to their sudden cardiac death, the vast majority of these were patients with known heart disease and were seen for routine or evidently unrelated reasons. While the classical

"premonitory symptoms" of chest pains, "gastrointestinal symptoms" and "musculoskeletal symptoms" have been found, fatigue and unusual dyspnea seem to be emerging as possible premonitory symptoms. There is some evidence that those who drop dead instantly - in contrast to those who die in 5 minutes or longer - have had fewer premonitory symptoms prior to their acute event.

The pathophysiology of sudden cardiac death and the onset of myocardial infarction is being examined in a number of ways. Ventricular fibrillation has been found the major cause of sudden cardiac death from two lines of evidence which buttress the clinical basis for this mechanism - the common finding of ventricular fibrillation by emergency rescue teams when persons are seen minutes after their collapse (in contrast to cardiac standstill which is more commonly observed after longer delays), and the observation that almost half the persons who are defibrillated and completely resuscitated by emergency rescue teams show no electrocardigraphic, enzyme, or other clinical evidence of having sustained fresh myocardial infarction, data based on almost 100 such complete resuscitations. Clinical-pathological correlations of sudden cardiac death are underway in four centers with the cooperation of the medical examiner's offices; deaths are studied which occur within 24 hours of onset of acute symptoms in persons less than 65 years of age without known or symptomatically advanced heart disease. Of over 700 cases, approximately 30% are in persons found dead (unobserved); about 1/3 of the balance appear to die "instantaneously" (i.e., within one or two minutes of the onset of symptoms), an additional 1/3 within the first hour, and the final 1/3 within the balance of 24 hours. Most, but not all, victims have extensive coronary artery disease, 1/3 have scars of old infarctions, and approximately 10% have acute myocardial infarction which histologically antedates the acute symptoms. Cardiomegaly and hypertensive heart disease are common. Acute thrombi of major coronary arteries are present in only a minority of cases and seem to be particularly rare in "instantaneous" cardiac death.

The electrophysiological correlates of risk factors cited previously provide inferential information about some pathophysiological mechanisms. Studies of exercise electrocardiograms in large populations (over 1,000 per year) and community-wide studies of all coronary angiograms have been initiated for long-term follow-up. To determine whether the stages of sleep of patients play a role in the generation of arrhythmias, techniques have been developed for the acquisition and automatic reduction of electroencephalographic signals and their correlation with electrocardiographic and blood pressure variations. To facilitate large-scale, long-term assessment of the cardiac rhythm continuously and of the responses to therapy, computer programs have been developed to permit a rapid (60 times real time) off-line analysis of electrocardiographic records with particular emphasis upon variations in QRST morphology; the initial studies on observations following acute myocardial infarction and drug therapy are being expanded to include assessment before and after coronary artery bypass surgery. A study in the animal laboratory is assessing the effects of temporary coronary occlusion and

reperfusion, as well as of temperature changes upon rhythm disturbances, especially ventricular fibrillation.

Therapy to prevent sudden cardiac death has been undertaken from several directions. The use of specially-equipped ambulance systems in three centers has not only provided information on the early pathophysiology of myocardial infarction and sudden cardiac death but has demonstrated the feasibility of training paramedical personnel to make significant observations and judgments when confronted with patients with cardiovascular emergencies, to obtain electrocardiographic signals for transmission, to administer emergency electrical defibrillation, and to administer intramuscular and intravenous medications in addition to the conventional cardiopulmonary resuscitative maneuvers. In one of the communities over a two year period, 94 patients were successfully resuscitated - 60 from ventricular fibrillation which was present at the time of arrival, and 34 from additional causes; residual brain damage has not been a problem. Emergency teams stationed in large athletic stadia have also been effective in saving lives, but the frequency of cardiovascular collapse has not been found to be as great as expected. Both in the ambulances and in the stadia, these studies have demonstrated the advantage and need for a comprehensive emergency system which is capable of managing cardiovascular problems, rather than for unique cardiovascular teams.

Recognizing that the majority of persons who die with coronary heart disease do so apparently of ventricular irritability and fibrillation in the first minutes and hours after the onset of symptoms, frequently before reaching medical care, a study is underway to evaluate the effects of antiarrhythmic agents which can be self-administered by a rapidly-acting route - lidocaine and atropine. Preliminary pharmacokinetic studies show that 300 mgm of lidocaine given intramuscularly results in plasma levels in excess of 1 mgm per liter within 10 minutes; intramuscular atropine raises heart rate by an average of 25% beginning within 10 minutes after injection. Studies in patients with suspected acute myocardial infarction have been initiated in an extensive ambulance system and are soon to be implemented in the coronary care units of two hospitals to assess prophylactic administration on a random basis of intramuscular atropine or placebo in the face of bradycardia, or lidocaine or placebo at heart rates in excess to 60. The effects of these drugs when given for specific indications are also being systematically evaluated. In a separate study the effects of lidociane are being determined in patients with acute myocardial infarction and pre-existing disturbances of atrioventricular conduction, a circumstance in which the safety of this drug has not yet been ascertained.

In addition to the studies on early therapy following the onset of symptoms, two others are being conducted to evaluate the effects on arrhythmias of prophylactic therapy with antiarhythmic drugs and of coronary artery surgery performed primarily for refractory angina pectoris. The effects of the surgical procedure in patients with unstable angina are being studied in a collaborative randomized, controlled study in six Myocardial Infarction Research Units and one additional center.

Cornell University Medical Center

Contract No. NIH-70-2069
Contract Amount: $511,970 (5-11-70 to 5-10-72)
Principal Investigator: Lawrence Hinkle, M.D.

A long-term prospective study of sudden cardiac death is being conducted. Physical exams, ambulatory 24-hour EKG recordings, and various laboratory studies are conducted periodically on 300 high risk patients and 100 controls from a population of varying socioeconomic levels. Prognostic value of arrhythmias, heart rate during life patterns and other risk factors are being assessed. Over 300 patients have been entered to date and the second round of follow-up exams is now being completed. Most sudden deaths have occurred in men with clinically evident coronary heart disease, but approximately 1/3 of sudden deaths have occurred among men with hypertensive cardiovascular disease or chronic obstructive pulmonary disease. A slow heart rate and a low peak rate response to exercise, "sustained relative bradycardia", seems to represent a newly recognized risk factor. Transient disorders of cardiac conduction occur among many asymptomatic men; many of these men later develop sustained disorders of conduction which increase the risk of sudden death. Frequent ventricular dysrhythmias are associated with an enhanced risk of sudden death.

Emory University

Contract No. NIH-70-2070
Contract Amount: $32,768 (4/1/70 to 5/31/72)
Principal Investigator: Nanette Wenger, M.D.

Sudden cardiac death is being investigated by special cardiac resuscitation teams stationed at two major athletic stadia in Atlanta, Georgia. The objectives have been to obtain early physiological data from patients sustaining acute cardiac events and to assess the feasibility of such emergency teams for large crowds. Sudden cardiac death was not encountered as frequently as was anticipated but a substantial fraction of such patients were successfully resuscitated by well-trained non-medical personnel, a few physicians, and the use of simple, relatively inexpensive equipment. A variety of major medical emergencies were encountered in addition to sudden cardiac death due to arteriosclerotic heart disease.

Johns Hopkins University

Contract No. NIH-70-2071
Contract Amount: $322,000 (4-15-70 to 5-10-72)
Principal Investigator: Lewis Kuller, M.D.

This group is one of the four participating in the collaborative necropsy-history study. All sudden cardiac death cases from an area of Baltimore City with an approximate population of 500,000 are studied. Approximately 320 cases have been characterized with complete clinical and pathological data. Approximately 1/2 of sudden deaths have prior history of heart disease, and there is a high frequency of previous hypertension and diabetes. Sudden death has been found to be a rare phenomenon in Negroes without a prior history of these conditions. A high percentage of patients with sudden cardiac death and those surviving myocardial infarction have prodromal symptoms, but fatigue is unexpectedly common among those with sudden death. No special precipitating events have been noted. The most common pathologic finding has been severe diffuse atherosclerosis of the coronary arteries; single vessel disease is a very unusual cause of sudden death. Increased heart weight was a common pathologic finding. Only 9% of sudden deaths had a fresh myocardial infarction. Significant disease of the smaller intramyocardial branches of coronary arteries is rare. About 1/3 of the victims had a fresh or organizing coronary thrombosis. When a thrombosis was noted, there was always a history of significant previous symptomatology.

University of Miami

Contract No. NIH-70-2072
Contract Amount: $455,643 (6/1/70 to 5/10/72)
Principal Investigator: Eugene Nagel, M.D.

This group is one of the four participating in the collaborative necropsy-history study. Over 100 cases have been completed and a comparable number are pending completion. An additional major activity is utilizing the fire department rescue squads for the early acquisition of physiological data in patients with suspected acute myocardial infarction or apparent sudden cardiac death, as well as for the development and application of more effective means of early therapy. Sixteen hundred telemetered electrocardiograms have been monitored. In both patients with acute myocardial infarction and those with acute ischemic episodes, approximately 15% are found to have bradycardia. Defibrillation was attempted in 126 patients yielding 21 long-term survivors, i.e., admitted to and discharged alive from the hospital. In long-term survivors from defibrillation, 36% did not have an acute myocardial infarction. Flail chest and aspiration pneumonia have been the most common complications of the resuscitation process. To achieve these results, improvements in communications systems were implemented and 46 paramedics were trained and certified in advanced resuscitation techniques.

Mt. Zion Hospital (San Francisco)

Contract No. NIH-70-2073
Contract Amount: $144,887 (2-27-70 to 5-10-72)
Principal Investigator: Meyer Friedman, M.D.

This group is one of the four participating in the collaborative necropsy-history study. Ninety-seven cases of sudden cardiac death have complete clinical data, and these have been transposed onto computer coded forms. These investigators have found the Type A behavior pattern in the vast majority of patients with sudden cardiac death, as well as in patients hospitalized with myocardial infarction. They have also found that in patients who die almost instantaneously after the onset of acute illness, the incidence of prodromal symptoms is much lower and no acute coronary thrombus or infarction has been found in any of their twenty cases.

Ohio State University

Contract No. NIH-70-2074
Contract Amount: $258,000 (6-22-70 to 6-21-72)
Principal Investigator: Joseph Robert Anthony, M.D.

This group is one of the four participating in the collaborative necropsy-history study. It also serves as the central coordinator for the computer analysis of the pooled data. A common clinical and pathological protocol for data collection has been developed. To date, this group has over 150 cases of sudden cardiac death with complete clinical and pathological data. In 80% of the victims of sudden cardiac death, the death occurred within an hour of the onset of acute symptoms. Fifty percent of the victims had a fresh coronary artery occlusion, whereas only 20% had evidence of a recent myocardial infarction. Nearly 2/3 of the subjectives had the onset of their symptoms witnessed by another person, implying a possible approach for early treatment.

University of Washington

Contract No. NHLI-71-2474
Contract Amount: $252,638 (6-30-71 to 6-29-72)
Principal Investigator: Harold T. Dodge, M.D.

Sudden cardiac death is being studied in several ways. Patients resuscitated from ventricular fibrillation outside the hospital by emergency rescue teams of the fire department subsequently undergo stress

electrocardiography, ambulatory EKG monitoring, coronary arteriograms and long-term follow-up; some will receive antiarrhythmic agents. Over 500 electrocardiograms obtained during graded exercise testing of middle aged persons have been assessed with the aid of computer analysis for risk factors for sudden cardiac death. In all patients in the community undergoing coronary angiography, correlations are made with stress electrocardiography and with ultimate long-term follow-up. In persons sustaining sudden cardiac death, clinical-pathological correlations are being conducted. Sixty patients have been resuscitated from ventricular fibrillation by the emergency rescue teams. Almost half of these patients do not have a detectable acute myocardial infarction.

Kaiser Foundation Research Institute (Oakland)

Contract No. NIH-71-2477
Contract Amount: $89,900 (6-16-71 to 6-15-72)
Principal Investigator: Gary D. Friedman, M.D.

This project is a retrospective epidemiological study using the Kaiser-Permante Multiphasic Examination data base on 100,000 middle-aged persons to search for characteristics other than the known "coronary risk factors" that might predispose to or predict the development of either myocardial infarction or sudden cardiac death. In the first year investigators have identified and documented approximately 450 cases of acute myocardial infarction and 250 cases of sudden cardiac death. Three control groups will be provided from the pool of data on 100,000 patients. Numerous computer analyses will be performed in the second year, comparing index cases and controls in search for new risk factors.

Health and Hospitals Governing Commission of Cook County (Ill.)

Contract No. NHLI-71-2478
Contract Amount: $140,000 (6-30-71 to 6-29-72)
Principal Investigator: Kenneth Rosen, M.D.

Atrial pacing and His bundle recordings are being used to study the prognosis for sudden cardiac death in patients with chronic bifasicular block. A subset of high risk patients will be defined and treated with prophylactic demand pacing. To date, a total of 99 new patients have been studied with complete electrophysiological data. A conduction disease clinic has been established and is functioning effectively. The forms for the initial clinical and electrophysiological data as well as follow-ups have been designed and data on all the patients have been key-punched and entered into a data bank suitable for computer analysis. Five patients entered in the study have died, one of these suddenly. Examination of the conduction systems is being performed.

New England Medical Center Hospitals

Contract No. NIH-71-2479
Contract Amount: $58,530 (6/30/71 to 6/29/72)
Principal Investigator: Herbert J. Levine, M.D.

This project seeks to characterize the electrophysiological and mechanical characteristics of the dog heart during the phase of recovery from regional myocardial ischemia, using this as a model for the pathogenesis of arrhythmias which could in humans lead to sudden cardiac death. The ultimate goal is to design antiarrhythmic interventions to diminish or eliminate the arrhythmias which follow temporary coronary occlusion. Results to date include observations on the differential effects of the duration of coronary ligation on the electrophysiology of the ventricle: following ligation, there is an acute high incidence of arrhythmias which decreases with time; on the other hand, the incidence of arrhythmias following release of ligation is directionally correlated with the duration of the temporary coronary occlusion. In addition, the temperature of the ischemic myocardium is found to decrease significantly during ligations, in proportion to the duration of ischemia. In the second year, the investigators will explore possible mechanisms for these phenomena by the development of computer techniques to permit evaluation of the dispersion of refractory periods; by the use of heat exchangers and intraventricular thermistors to evaluate the role of changes in temperature; and by the addition of pressure and tension measurements to correlate with the electrophysiologic events.

Baylor College of Medicine

Contract No. NIH-NHLI-71-2480
Contract Amount: $137,594 (6-30-71 to 6-29-72)
Principal Investigators: Henry D. McIntosh, M.D., Peter Kellaway, Ph.D.

The relationship of changes in blood pressure and cardiac rhythm in certain phases of sleep to the development of ominous and potentially lethal arrhythmias are being examined in persons known to have coronary disease so that programs of prophylactic treatment may be designed. The automated system for data acquisition and analysis of ECG and EEG data in correlation has been devised and assembled, providing a unique tool for continuous and prolonged study of these aspects of cardiovascular and central nervous system function. Clinical studies have now been initiated to determine if potentially fatal arrhythmias are more likely to occur during certain phases of the sleep cycle. If definite relationships between sleep cycles and arrhythmias are demonstrated, future studies will attempt to define the rational use of drugs which modify the sleep cycle as well as of antiarrhythmic drugs such as xylocaine.

Washington University

Contract No. NHLI-71-2481
Contract Amount: $235,671 (6-30-71 to 6-28-72)
Principal Investigator: G. Charles Oliver, M.D.

Ambulatory, periodic, long-term EKG recordings with off-line computer analysis are being used to study ventricular arrhythmias in patients with known coronary heart disease, as well as controls. In the first year, effort has been focused on development of computer methods for rapid, automatic off-line analysis of electrocardiograms and on pilot studies for prophylactic therapeutic trials. Hardware and software are being developed to permit data analysis at 60 times real time. Emphasis has been placed on recognitions of subtle variations on the QRST complex. Thirty-three patients with documented infarctions have entered this study to date. One-third of the patients monitored showed no PVC's. The remaining two-thirds show PVC's with varying degrees of severity.

Leland Stanford Jr. University

Contract No. NIH-71-2482
Contract Amount: $80,991 (6/30/71 to 6/29/72)
Principal Investigator: Donald C. Harrison, M.D.

Patients who enter the Stanford University Hospital with the syndrome of "unstable angina" or "pre-infarction" are studied thoroughly to characterize this syndrome in terms of hemodynamic, electrocardiographic, and arteriographic measurements. A special-studies room has been designed and equipped in the coronary care unit, and approximately 20 patients have been studied. Early findings indicate significant correlations between the occurrence of pain and hemodynamic and electrocardiographic measurements. Coronary arteriography has been conducted without incident in these patients, and reveals extensive coronary atherosclerosis. Preliminary results indicate these patients have a significant risk (15-20%) of subsequent infarction and sudden death in the first six months following presentation. Longer-term studies and more patients will be required to establish more precisely the level of risk. Early data indicate these patients are likewise at substantial risk when undergoing coronary artery vein bypass surgery. The Stanford group has participated in all stages of the design of the collaborative study of medical and surgical therapies of "unstable angina" in the Myocardial Infarction Research Units, and will be participating in the study in the coming year.

Survival Technology, Inc. (Bethesda, Md.)

Contract No. NIH-71-2515
Contract Amount: $26,500 (6-16-71 to 6-15-72)
Principal Investigator: Stanley Sarnoff, M.D.

Survival Technology, Inc., assists in coordinating the collaborative study of the effects of intramuscular atropine and lidocaine given early in the course of patients with symptoms of an acute myocardial infarction. They also supply some of the drugs in automatic intramuscular injectors.

Meadowbrook Education and Research Foundation, Inc. (Nassau County, N.Y.)

Contract No. NIH-71-2518
Contract Amount: $9,000 (6/30/71 to 6/29/72)
Principal Investigator: Costas T. Lambrew, M.D.

This project is part of the collaborative study of the effects of intramuscular atropine and lidocaine early in the course of patients suspected of an acute myocardial infarction. During the first year of this project in cooperation with the Nassau County Police Department Rescue Service and the State University of New York Medical School at Meadowbrook, the ambulances have been outfitted with equipment for telemetering ECG signals and the drivers trained in advanced rescue techniques, including those needed to provide special care for patients suspected of having an acute myocardial infarction. A protocol has been implemented for the prophylactic administration on a random basis of intramuscular atropine/placebo or lidocaine/placebo to patients suspected of having myocardial infarction. ECG signals are telemetered continuously, and paramedical personnel are supervised in all phases via telemetry by a physician. Results to date are preliminary.

Yale University

Contract No. NIH-71-2519
Contract Amount: $13,800 (6/30/71 to 6/29/72)
Principal Investigator: Lawrence Cohen, M.D.

This project is part of the collaborative study of intramuscular atropine and lidocaine administered early in the course of patients with symptoms of an acute myocardial infarction. Patients admitted to the coronary care unit with these symptoms and without contra-indications receive atropine or placebo (in the presence of bradycardia) or lidocaine or placebo (in the absence of bradycardia). Results to date are only preliminary.

University of Pennsylvania

Contract No. NIH-71-2521
Contract Amount: $15,318 (6/30/71 to 6/29/72)
Principal Investigator: John A. Kastor, M.D.

This project is part of the collaborative study of the effects of intramuscular atropine and lidocaine early in the course of patients suspected of an acute myocardial infarction, to determine whether these drugs are effective in preventing or treating arrhythmias or in decreasing mortality. Preliminary studies have been completed of the pharmacokinetics of atropine given intramuscularly, and standard doses have been established. A response of the heart rate to atropine and effective serum concentrations of lidocaine are achieved early. Results at this point are prelininary.

Montgomery County (Md.) Heart Association

Contract No. NIH-71-2485
Contract Amount: $30,000 (6/25/71 to 6/24/72)
Principal Investigator: Barton J. Gershen, M.D.

Patients with symptoms of a myocardial infarction are seen in the Montgomery County Heart Association's emergency heart mobile and treated by a nurse and trained paramedical personnel under the radio supervision of a physician. The incidence of bradycardia (heart rate less than 60/min.) and the incidence of hypotension were determined, and the effects of intramuscular atropine studied in these patients. In 84 patients with myocardial infarction, bradycardia and hypotension coexisted in 6%, bradycardia alone was present in 18% and hypotension alone in 6%. Half the patients with bradycardia and 80% of those with bradycardia and hypotension received atropine; all responded with an increase in heart rate and blood pressure rose in those with both bradycardia and hypotension. Overall mortality was 8%; however, all patients with bradycardia survived to leave the hospital, both those treated and those not.

Binnengasthuis Hospital (Amsterdam)

Contract No. NIH-72-2907
Contract Amount: $9,500 (5/31/72 to 5/30/73)
Principal Investigator: A.J. Dunning, M.D.

The effects of intramuscular lidocaine on atrioventricular conduction will be studied in patients with acute myocardial infarction who develop advanced atrioventricular conduction disturbances, a circumstance in which the safety of the drug has not yet been established. The effects of lidocaine will be correlated with plasma levels of the drug. Patients will be studied while undergoing catheterization for placement of pacing catheters as part of their clinical care.

SUDDEN CARDIAC DEATH - PORTABLE AUTOMATIC ELECTROCARDIOGRAPHIC AND BLOOD PRESSURE DATA ACQUISITION AND CENTRAL DATA ANALYSIS SYSTEM

Variations in the cardiac rhythm and in the blood pressure of ambulatory persons are felt to be potentially important in identifying those at high risk for sudden cardiac death, for characterizing potential pathophysiological mechanisms, and for assessing the efficacy of therapeutic interventions. To obtain apparatus which will permit study of these phenomena, a request for proposals was distributed for obtaining and recording the electrocardiogram continuously and the blood pressure intermittently and automatically in ambulatory persons, and for the apparatus to permit the rapid automatic analysis of these recorded data. Nineteen proposals were received in response to this solicitation and it is anticipated that a contract will be awarded early in the coming fiscal year.

ACUTE MYOCARDIAL INFARCTION - MYOCARDIAL INFARCTION RESEARCH UNITS

Over the past year the major program goal of the nine Myocardial Infarction Research Units (MIRUs) has continued to be the better understanding of acute myocardial infarction with particular emphasis on the underlying causes, clinical manifestations and optimum management. Results from the ongoing research projects have had a significant impact on the concepts and management of acute myocardial infarction.

The major focus of research has been in the clinical area. These studies encompass a wide range of subjects related to acute myocardial infarction which include clinical characterization, prognostic factors (natural course of the disease), therapeutic interventions and new methodology. They involve cardiac physiology, enzymology, electrophysiology, respiratory physiology, biochemistry, hematology, surgery, pathology, pharmacology, radiology, psychology, nuclear medicine and computer sciences.

The hemodynamic studies have shown the differences between right and left ventricular filling pressures, the disparity of function between the two ventricles and descriptions of ventricular function. Changes in compliance in the earliest hours and days after acute infarction have been shown to account for much of the early increases in ventricular filling pressures. The correlations between clinical class and these hemodynamic measurements show some disparities especially in those clinically uncomplicated patients who may have elevated ventricular filling pressures, low cardiac outputs, increased peripheral ventricular resistances, and/or low arterial oxygen tensions. Various possible prognostic indicators have been analyzed in detail for their short and long term significance. In general, clinical characterization alone has been shown to be quite reliable for determining in-hospital course. Hemodynamic descriptors, however, are of added benefit.

Elevated left ventricular filling pressures, cardiac work indices less than 1.7 $KgM/min/M^2$, and widened $A\text{-}VO_2$ differences have each been correlated with a poorer prognosis. Initial hemodynamic and clinical descriptors with in-hospital and post-hospital course are being pooled from all nine MIRUs. This combined data is being used to develop widely applicable descriptors for various subgroups which can be used in trials of specific therapeutic interventions.

Studies in clinical enzymology have received special attention in the past year. More reproducible and easily measured serum assays of isoenzymes of CPK have been developed in the MIRU and appear to be very specific for cardiac muscle damage. The ready availability of these qualitative and quantitative assays markedly increases the sensitivity and specificity for the diagnosis of acute myocardial infarction, even with equivocal ECG changes and in the presence of major surgery or other sources of CPK enzyme from skeletal muscle, liver, or lung damage. This test provides a rapid, more precise diagnosis of acute myocardial infarction with more accurate timing of onset.

The magnitude of total CPK appearance in serum has been developed and tested in MIRU animal studies as an indicator of infarct size, and is now being evaluated clinically. A close correlation between infarct size calculated from analyses of the enzyme curves and infarct size determined by more direct methods has been demonstrated and the relationship between clinical prognosis and infarct size reported. The power of this technique of enzyme curve analysis will be further enhanced by quantitative assays of the cardiac specific enzymes.

Another clinical use of the new enzyme curve analysis technique developed in the MIRU has been the determination of changes in infarct size. Continuing muscle damage can be discriminated from stable completed infarctions, and the effects of various therapeutic interventions have been determined directly on the amount of muscle damaged. For the first time a wide range of clinical interventions can now be tested for their direct effect on myocardial infarctions. Using this technique in animals the beneficial effects of circulatory assist, glucose-potassium-insulin infusion and increasing perfusion pressure have been shown, while decreased perfusion pressure, increased contractility or increased heart rate have increased infarct size. Previously, such interventions would have required prohibitively extensive clinical trials with large patient numbers and long term follow-ups for any measure of therapeutic effectiveness. This new MIRU development has added a whole new perspective to the management of patients with acute myocardial infarctions and already has markedly altered presently accepted modes of therapy.

In the field of dysrrhythmias, automated continuous rhythm analyses and QRS morphology by computer have been implemented clinically. This capability will be markedly expanded in the coming year and made more feasible for routine clinical monitoring of patients and evaluation of therapeutic interventions. Studies have demonstrated the significance of various arrhythmias and conduction disturbances which occur spontaneously or are induced by intracardiac pacing. Many of these studies have utilized direct His bundle recordings for more detailed analyses. From these MIRU studies revised indications for short and long term intracardiac pacing have been implemented. Also, a better description of significant arrhythmias during the acute disease course is now available.

A major emphasis has been placed on medical and surgical interventions. Continuous monitoring of pulmonary artery pressure and careful regulation of intravascular volume have become standard therapy for patients with heart failure or "shock" in the MIRUs as well as in other CCU's. Attempts are now being made to automatically control intravascular volume through servo-control mechanisms responsive to the pulmonary artery diastolic pressure. Other agents, with a direct effect on ventricular contractility, have been evaluated including dopamine, glucagon, isoproterenol, and digitalis. In other patients who present with an acute hypertensive syndrome associated with myocardial infarction, nitroglycerin, regitine, and ganglionic

blockers have been used to lower pressure, and have been shown to relieve cardiac failure, and protect myocardium. In addition, trials are continuing with the pharmacokinetics and clinical effects of antiarrhythmic agents during and after hospitalization. The therapeutic indications and method of administration of various antiarrhythmic agents have been demonstrated, such as procainamide, lidocaine, and bretylium.

In the most severely ill group of patients, the inter-MIRU cooperative trial with intra-aortic balloon assist is near completion. Initial results from this trial indicate the relative safety of this device, and its effectiveness in temporary reversal of the shock state in approximately 75% of patients. Unfortunately, alteration of long term survival in this study group with resistant cardiogenic shock and massive cardiac muscle loss has been disappointingly low.

The major focus of surgical studies is now on the effects of coronary artery bypass graft surgery. Intra-operative physiological information has been obtained at the time of graft placement, and pre- and post-operative evaluation of coronary anatomy and ventricular function have been correlated with the clinical course. Patients studied include those with chronic angina as well as patients with acute infarctions, unstable angina ("preinfarction syndrome", "impending infarction") and cardiogenic shock with and without intra-aortic balloon assist. A major effort has been directed at the planning and implementing of an inter-MIRU cooperative randomized trial of medical vs. surgical therapy for patients with unstable angina.

Various new methodologies developed in the MIRUs have been introduced into the clinical studies. One of the most widely utilized is the right heart flow directed balloon tip catheter. In the past year this catheter has been combined with capabilities for thermodilution cardiac outputs, intra-atrial electrograms, and non-radiologic placement of right ventricular pacing catheters. These newer modifications considerably increase the capabilities for hemodynamic and electrocardiographic monitoring of patients and their optimum management. To determine ventricular volume and wall motion even in the most acutely ill patient, ECG triggered radioisotope techniques developed in the MIRU have been used as well as echocardiography, radarkymography, and left heart dimensions. For the measurement of coronary blood flow, both continuous coronary sinus thermodilution (developed in the MIRU) and hydrogen infusion (refined under another Myocardial Infarction Program contract) are being evaluated clinically in the study of MIRU patients. Another new MIRU technique, which has proved very successful in the animal laboratories and is now undergoing extensive clinical trial, is precordial ST segment mapping for determination of changes in infarct size. Determination of oxyhemoglobin dissociation curves was introduced into MIRU studies in the past year.

The pathology sections have devoted a considerable amount of time to clinical pathologic correlation and implementation of a standard MIRU pathology protocol. MIRU patients who had cardiogenic shock have consistently demonstrated extensive muscle damage, as well as "shock lesions" in the peri-infarction region. These "shock lesions" are not present after reversal of the "shock state" with circulatory assist. Also, coronary thrombosis is usually present with pump failure whereas in the absence of pump failure thromboses are observed in less than one half of the cases. Other findings include a higher incidence of atrial and right ventricular infarct than had been recognized previously. Conduction system pathology and altered patterns of blood supply to nodal regions have been described. In addition to patient material, the pathologists have continued to provide morphologic support for many of the animal research projects.

In the various MIRU laboratory studies the major emphasis has continued to be on projects which have an immediate or a fundamental relevance to the clinical syndrome of acute myocardial infarction. Promising results of many laboratory projects are now being implemented clinically, such as serial enzymes and surface mapping for determination of infarct size and change in infarct size; cardiac output and coronary sinus blood flow by thermodilution; and the digitalis radioimmunoassays. Other significant findings have been developed and demonstrated in the laboratories. These include: cardiac beta receptor site isolation and identification; immunoassays for aldosterone; effects of coronary artery occlusion in atherosclerotic monkey models; CPK localization in cardiac muscle cells; effects of interventions on collagen formation in infarctions; excitation-contraction coupling; effects of oxygen supply on the uptake and exchange of potassium, calcium and magnesium in cardiac cells; effects of hypoxia and induced hypertrophy on synthesis and turnover of mitochondria and myofibrillar elements of the heart; the effects of drugs including antilymphocyte serum on wound healing; effects of mannitol on ventricular contractility, cell size and mitochondrial morphology; fibrinopeptide radioimmunoassays; changes in the coagulation and fibrinolytic system; renin-angiotensin system function; circulatory assist techniques; the von Bezold-Jarisch reflex; the pharmacology of morphine; changes in the coronary collateral circulation; regional myocardial blood flow determined with xenon, microspheres and endocardial beta detectors; imaging of infarctions with intravenously injected radioisotopes; various myocardial metabolism studies; and the effects of a wide range of pharmacological and hemodynamic interventions on infarct size.

In the data management sections, all nine digital computer systems are functioning. The five similar computers installed most recently have had extensive system programming in the past year. Application programs are available for bedside entry and retrieval from patient data files, determination of cardiogram and thermodilution cardiac outputs,

statistical processing, ST segment mapping, blood gas calculations and arrhythmia analyses. The four other units have had different computer system with different capabilities for a longer period of time. Special programs such as determining cardiac output and peripheral resistance from the aortic pressure pulse contour, automated pulmonary artery pressure measurements, echocardiographic analysis, and coronary angiographic scanning techniques have been developed on these computers. The computers can now give on-line evaluations of therapeutic intervention which permits studies not previously possible. In addition, information in patient files is immediately available at the bedside for clinical research or patient management. The automated analyses of ST segments and enzyme curves give on-line information about direct effects of interventions on infarct size. The automated echocardiographic readout permits standardization of this valuable but previously non-quantifiable data. The x-ray scanning techniques are used for on-line calculation of myocardial segment changes seen on biplance coronary arteriograms which previous required days for analysis.

In the past year results from the MIRU studies have appeared in numerous scientific journals and have been presented at many national and local meetings.

MIRU investigations have had a major impact on the problem of acute myocardial infarction and clinical research in cardiology. Myocardial infarction is now considered a dynamic process which can be influenced. The increased knowledge about the pathophysiology of myocardial infarction and determination of changes in infarct size provides important endpoints for the evaluation of promising therapeutic interventions clinically and in the animal laboratory. Attempts to intervene earlier in the course of the disease before irreversible muscle damage occurs are now possible and represent a major goal.

University of Alabama

Contract No. PH 43-67-1441
Contract Amount: $3,199,071 (6/29/67-6/28/72)
Principal Investigator: Charles E. Rackley, M.D.

A major interest at this unit has been the hemodynamic characterization of the complicated acutely ill patient with myocardial infarction. These studies have focused on the effects of volume infusion, alteration of ventricular function curves, and correlations with echocardiogram. Wherever possible these studies are being repeated at 6-12 months after hospital discharge when ventriculograms and coronary arteriograms are also obtained. Other patient studies include the effects of coronary

artery bypass graft surgery, surface dipole mapping, and blood supply of the human His bundle. In the laboratory, studies are directed at the effect of morphine sulfate and fatty acids on electrical and mechanical functions of the heart. Computer applications include hemodynamic monitoring, echocardiographic analysis, statistical programs, and data acquisition and retrieval.

University of California at San Diego

Contract No. PH-43-68-1332
Contract Amount: $2,928,595 (6/20/67-6/27/72)
Principal Investigator: John Ross, Jr., M.D.

A major focus at this unit has been on the measurement of myocardial infarct size, and factors which influence infarction. These studies, which are active in the animal laboratory and clinical research area, use tissue and serum assays of enzymes and epicardial and chest surface mapping. Factors which have been shown to have significant effects include heart rate changes, alterations in aortic pressure and contractility, circulatory assist, norepinephrine, isoproterenol, digitalis, glucose-potassium-insulin, reperfusion, and hypothermia. In addition in the MIRU clinical area they have demonstrated ventilation-perfusion abnormalities by xenon isotope techniques, changes in myocardial performance with radarkymography and radioisotope angiocardiograms, significance of changes in left heart dimensions, changes in oxyhemoglobin dissociation curves, and physiological effect of coronary artery surgery. Pathology provides clinical-pathological correlations and morphologic support for animal studies. In the laboratory they have also demonstrated changes in coronary blood flow and the collateral circulation after coronary artery ligation. The dedicated digital computer provides on-line blood gas analysis, on-line hemodynamic monitoring, discrete data filing and retrieval, statistical analysis, calculation of serum enzyme appearance and clearing, and analysis of the total oxyhemoglobin dissociation curve.

Cedars-Sinai Medical Center

Contract No. PH-43-68-1333
Contract Amount: $2,698,072 (6/28/68-6/27/72)
Principal Investigator: H.J.C. Swan, M.D.

A major achievement at this unit has been the design and various modifications of a flow directed right heart balloon tip catheter. This development of a means for a simple bedside technique permitting measurement of pulmonary artery pressures, pulmonary capillary wedge pressure and thermodilution cardiac outputs has been a significant advance and an aid for this unit as well as other institutions involved in clinical research and patient care. The coronary sinus blood flow measurements with continuous

thermodilution developed at this unit represent a new repeatable method for clinically determining myocardial blood flow. Their two bed clinical research area has been mainly dedicated to the study of complicated acute myocardial infarction patients. The clinical research studies have demonstrated the effects of glucagon, responses to "stress tests", alterations in ventricular compliance, myocardial force-velocity relations, the significance of acute chest x-ray changes, acute changes in cortisol, catecholamines and free fatty acids, responses of the peripheral circulation, effects on coronary artery bypass graft surgery, and a hypercontractile response to acute infarction. In the laboratory new modifications of intra-aortic circulatory assist have been designed and tested, pressure volume relationships have been analyzed, and changes in myocardial potassium with arrhythmias described. The computer system provides on-line hemodynamic monitoring, rapid storage and retrieval of discrete data and various statistical programs.

University of Chicago

Contract No. PH 43-68-1334
Contract Amount: $1,847,415 (6/28/68-6/27/72)
Principal Investigator: Leon Resnekov, M.D.

A major goal of this MIRU has been to correlate changes at the tissue, cellular, and subcellular level with the clinical characterization of patients with acute myocardial infarction. Studies in the two bed clinical unit have described arrhythmias and QRS morphology from continuous computer analysis, ventricular contractile responses, the correlations between clinical and hemodynamic measurements, the effect of atrial overdrive on intractable dysrrhythmias and the actions of digitalis. In the laboratories coronary ligation and mercury embolization models have been used to show differences between right and left ventricular function, effects of theophylline and isoproterenol, and tissue activity of cyclic 3,5-AMP. Other laboratory projects have demonstrated excitation-contraction coupling using potassium contracture and voltage clamp methods, the basic relation between membrane voltage and tension development, the effects of cooling and reperfusion on electrical properties of heart muscle cells, the effect of oxygen supply on the uptake and exchange of potassium calcium and magnesium, and the effects of hypoxia and induced hypertrophy on synthesis and turnover of mitochondria and myofibrillar elements of the heart. The computer provides in addition to arrhythmia monitoring, real time programs for analysis of hemodynamic parameters, collection storage and analysis of clinical data and a problem-oriented record system.

Cornell Medical Center

Contract No. PH-43-67-1439
Contract Amount: $2,836,267 (2/26/67-2/25/72)
Principal Investigator: Thomas Killip, M.D.

The major objective of this unit has been the study of the complicated acutely ill patient and factors which might be earlier indications of clinical deterioration. Patient studies are performed in a special two bed unit adjacent to the CCU. Studies in this clinical area have shown the etiology and significance of hypoxemia in acute infarction, trans-myocardial biochemical changes, the significance of digitalis serum levels, the pharmacokinetics of intravenous and intramuscular lidocaine, the prognostic significance of changes in cardiac work and the effect of intra-aortic counterpulsating balloon in cardiogenic shock. In the laboratory the effects of substrate manipulation on experimental myocardial infarction have been demonstrated. The pathology studies have shown significant clinical pathologic correlations which includes not only the importance of infarct size but also the varying age of infarctions within a single area. The computer provides on-line hemo-dynamic monitoring, patient admission and summary data, and a file system for rapid storage and retrieval of data.

Duke University Medical Center

Contract No. PH 43-67-1440
Contract Amount: $3,555,074 (6/28/67-6/27/72)
Principal Investigator: James J. Morris, M.D.

The major objective of this unit has been the correlation of admission clinical and hemodynamic data with the subsequent in-hospital and post-hospital course. An 85% accuracy in determining subsequent course has been achieved. Other clinical studies have shown the effects of furosemide and oxygen administration; a high specifity and sensitivity of CPK isoenzymes for the diagnosis of infarction; the importance of atrial contribution to ventricular filling in acute infarctions; the significance of transient and permanent conduction defects; the changes in fibrinogen, lytic activity and partial thromboplastin time as a response to and not a cause of myocardial infarction; and coronary artery anatomy and segmental myocardial contraction determined from coronary cineangiograms. Surgical studies have demonstrated the physiologic responses to occlusion of bypass grafts and local infusions of drugs, as well as responses in the immediate postoperative period. Pathology studies have shown the incidence of coronary thrombosis, changes in the conduction system, new methods for sizing infarctions and a high incidence of right ventricular infarctions. In the laboratory new methods for determining isoenzymes have been developed and responses of hormones and clotting system to acute infarctions in animals have been described. The computer system provides real time hemodynamic monitoring, continuous analyses of aortic pressure pulse curves and a variable length data file system with capabilities for rapid storage and retrieval of data. Admission and follow-up data from all nine MIRUs have been entered into this computer.

Johns Hopkins Hospital

Contract No. PH 43-67-1444
Contract Amount: $2,281,956 (6/29/67-6/28/72)
Principal Investigator: Richard Ross, M.D.

A major impact of this unit has been the introduction of radioisotope techniques into the clinical studies and undertaking a prospective randomized comparison of the effects of medical and surgical therapy in unstable angina. Patients in the two bed unit have hemodynamic and radioisotope evaluations with responses to drugs evaluated. Clinical studies have shown the responses to pacing, volume loading, dopamine, norepinephrine, free fatty acid elevations, and routine patient activities. Coronary anatomy has been determined from coronary cineangiocardiograms in chronic and unstable angina and post acute infarction. The effects of surgery in unstable angina are being evaluated. Laboratory studies have shown changes in regional myocardial blood flow as assessed by xenon, microspheres, and catheter tip beta detector techniques. Other studies are examining the effects of free fatty acids, infarct images with K^{43}, and the intracellular localization and release of creatine phosphokinase during myocardial infarction. Pathology gives clinical pathological correlations. The computer provides real time hemodynamic monitoring.

Massachusetts General Hospital

Contract No. PH-43-67-1443
Contract Amount: $3,450,589 (6/29/67-6/28/72)
Principal Investigator: Charles A. Sanders, M.D.

A major emphasis at this unit has been on the study of cardiogenic shock. Patients with circulatory assist have been evaluated in their special intensive study room. Other invasive studies in less acutely ill patients are performed in a second study room, while randomized double-blind trials with antiarrhythmic agents are carried out in the adjacent CCU. Other patient studies are being undertaken in the operating room, catheterization laboratory, and second CCU and have shown psychological changes, the optimum length of hospital stay, pulmonary ventilation perfusion changes, premature airway closure, changes in pulmonary extravascular water, natural history of unstable angina, and effects of nitroglycerin and bretylium. The biochemical laboratory has isolated and identified beta receptor sites in the heart, and has developed digitalis, aldosterone and fibrinopeptide immunoassays. The effects of mannitol in animals and changes in oxyhemoglobin dissociation in patients have been described. In pathology "shock lesions", effects of drugs on wound healing, and small vessel lesions have been evaluated. Computer applications include continuous arrhythmia analysis, hemodynamic monitoring, data acquisition and retrieval and statistical analyses.

University of Rochester

Contract No. PH 43-68-1331
Contract Amount: $2,331,500 (6/28/68-6/27/72)
Principal Investigator: Paul N. Yu, M.D.

Major objectives at this unit have been to describe the pre-hospital and in-hospital phases of the acute illness in the uncomplicated as well as complicated patient with acute myocardial infarction. The pre-hospital studies have shown the electrophysiological, biochemical and psychological correlates in the earliest stages of the acute infarction. The in-hospital studies have shown a 30% incidence of abnormal hemodynamics even in uncomplicated patients, the gradual normalization of abnormal findings without specific interventions, and the correlations between hemodynamics, ventilatory function and pulmonary extravascular water volume. Other clinical studies have demonstrated psychological changes during the acute and follow-up phase, the patterns of catecholamine excretion, the changes in systolic time intervals, the echocardiographic patterns, the effects of intra-aortic balloon counterpulsation and the correlation between the electrocardiographic P wave and left atrial pressure. The pathology studies provide clinical pathologic correlations with special emphasis on the nodal and conducting systems. In the laboratory, changes in collagen in infarction are being assessed. The computer has capabilities for on-line hemodynamic monitoring, multiple statistical programs, and a data file system which provides rapid entry and retrieval of patient information at the nurses station or bedside.

ACUTE MYOCARDIAL INFARCTION - QUANTIFYING INFARCT SIZE

A method to determine the amount of myocardium affected by infarction and/or ischemia is important for therapy and for clinical research in myocardial infarction. Such a method must be applicable safely to large numbers of patients, provide information on the natural progression of the disease, yield results rapidly and reproducibly, and be repeatable to monitor the impact of experimental and therapeutic interventions on the extent of myocardial damage. Because of this need, a program of research is being conducted to develop such a method. Two research projects are exploring a variety of established and new radionuclides and radiopharmaceuticals for "imaging" acute myocardial infarctions in patients. A third project is assessing the feasibility of new ultrasonic techniques for accurately detecting and sizing damaged myocardium.

An analogue of potassium, ^{129}Cs, is being produced for use in sizing infarcts in a non-invasive way. The production techniques of this nuclide are being refined, and the improved production (20-30 mCi per cyclotron "run") permits a brisk pace for experimental studies. At present, these investigators obtain scans in both dogs and man imaging infarcts 2 cm. in diameter in anterior and apical regions of the heart. They are working to optimize dosage, to improve resolution, and to extend their ability to "image" infarcts to other regions.

In another project, ^{129}Cs is also being used to image infarcts. In addition, organic molecules with a variety of radioactive labels are being studied to find better nuclides in terms of isotope energies, half-lives, contrast with background and frequent repeatability of studies. Clinical studies with each nuclide are conducted when the preliminary details have been worked out in animals.

The third project established under this sub-program is exploring the feasibility of using ultrasonic techniques to quantify infarcted or ischemic regions of myocardium in man. With the more promising technique of spectrum analysis in the frequency domain, it has been possible to distinguish damaged from normal skeletal muscle. With further refinements in instrumentation, studies are being performed to determine the efficacy of the technique in quantifying experimental infarction in the dog and the ultimate possibility of its application in man.

In addition to this special program, several MIRUs are exploring ways of sizing infarcts. Studies of the radionuclides ^{43}K and $^{13}NH_3$ are in the early stages and will be ready for application. Two new and promising methods for estimating the extent of myocardial damage have been developed for use in experimental animals and man. Epicardial unipolar electrodes are used to map out the extent of ST segment elevation in ischemia and/or infarction; serial serum and myocardial creatine phosphokinase (CPK) activities are assessed to estimate the degree and extent of myocardium affected. The ST segment method has been successfully modified in animal studies using precordial electrodes. This technique and that using serial serum CPK activity have been implanted in clinical studies.

University of California at Los Angeles

Contract No. NIH-71-2491
Contract Amount: $52,040 (6/30/71 - 6/29/72)
Co-Principal Investigators: Leslie M. Eber, M.D.
Norman D. Poe, M.D.

This project has investigated the properties of several radionuclides, including ^{43}K, ^{129}Cs, and ^{11}C-fatty acids, to find one which is optimal for imaging infarcted, ischemic, or scarred myocardium following intravenous injection in clinical situations. Initial studies are performed in dogs to determine the kinetics of the nuclides and to develop the techniques necessary for optimal imaging. Standard microsphere techniques have been used to provide comparative estimates of regional coronary perfusion. Studies to date reveal that ^{43}K is extracted much more rapidly, and is thus to be preferred for acute studies with intracoronary injections. ^{129}Cs persists much longer, and is thus better suited to clinical situations, where injections are made intravenously and several studies are needed over prolonged periods (greater than 24 hours).

Clear images of infarcts are not obtained with present techniques until almost 24 hours following infarction. Future experiments will explore improved dosages and imaging procedures to permit earlier imaging. Preliminary studies in patients with coronary artery disease have yielded scans with localized defects, but resolution is limited. Complicated "subtraction techniques" utilizing computer methods are needed and are being developed.

Simultaneously with developing these techniques, the investigators are exploring the promise of other, newer approaches, using fatty acids labelled with ^{11}C, ^{123}I, and ^{18}Fl in animal experiments, with human studies pending.

University of Cincinnati

Contract No. NIH-71-2489
Contract Amount: $59,948 (6/30/71 - 6/29/72)
Principal Investigator: Robert J. Adolph, M.D.

These investigators pioneered in the development of techniques for the production and use of ^{129}Cs prior to the inception of this contract. Since this program began they have improved techniques for production of ^{129}Cs and are now regularly achieving high-yield production runs (20-30 mCi) permitting a high rate of experimental investigations. They are conducting studies in dogs to establish the appropriate dosages and scanning procedures and to document the sensitivity and accuracy of the method; thus, with 4 mCi they can detect experimental apical

and anterior infarcts measuring at least 2 cm x 2 cm in diameters. Infarcts begin to be detectable 3 hours after ligation of the coronary artery and are clearly visible in less than 24 hours.

In preliminary clinical studies, 8 patients undergoing diagnostic coronary arteriography had scans performed. Two of these were found not to have significant atherosclerosis, and thus were "normals" with normal scans. Each of the other six had a history of old myocardial infarction and in each case the old infarct was detected by the scan and identified in the correct location. Current plans include progression of studies to patients with acute myocardial infarction.

Massachusetts Institute of Technology

Contract No. NIH-72-2017
Contract Amount: $40,800 (9/15/71 - 9/14/72)
Principal Investigator: P.P. Lele, M.D., Ph.D.

This project is a preliminary study to determine the feasibility of using ultrasonic techniques to detect and quantify myocardium which is ischemic or infarcted. Early results document that the acoustic reflectance and the characteristic acoustic impedence of infarcted myocardium are lower than those of normal myocardium. Techniques to assess these differences in terms of amplitude changes in the temporal domain were found not to be promising; they depend critically on the angle of incidence, and relatively small variations in the angle significantly alter the results obtained. However, analysis of reflected acoustic signals in the frequency domain are not dependent on precise angulation and are much more promising. Skeletal muscle necrotized by heat or by vascular occlusion has been unequivocally differentiated from normal muscle. Studies evaluating this technique are continuing in experimental infarction in animals to determine the feasibility of applying the technique ultimately to infarction in man.

PHYSIOLOGICAL AND BIOCHEMICAL PROCESSES FUNDAMENTAL TO NEW THERAPEUTIC METHODS PROTECTING ISCHEMIC MYOCARDIUM

The specific objective of this program is the development of interventions to protect ischemic myocardium, to minimize infarct size, and/or to enhance myocardial repair, including experimental studies of the physiology and biochemistry of ischemic myocardium and myocardial scar formation fundamental to the development of such interventions.

During this the first year of their contract operation, each of the contractors have acquired the necessary facilities, equipment, and personnel required for their project. Each has developed or obtained the most suitable animal model preparation for their individual needs and have resolved technical difficulties to give them reliable results. A significant milestone has been the development of a working isolated rat heart preparation in which controlled degrees of ischemic rather than just hypoxia can be developed. There has been considerable cooperation and interchange of ideas and techniques between the contractors on the animal model preparations. This cooperative spirit has now grown to include collaborative efforts between individual contracts on the research itself.

Progress toward the scientific objectives of the contracts have been made in the relatively short period of time to date. It has been found that in contrast to hypoxia which increases glucose utilization in association with depletion of high-energy phosphates, ischemia produces the same depletion of these vital energy supplies without a compensatory increase in glucose utilization. Intriguing biochemical and electron micrographic findings suggest that lysosomal activity may be inappropriately elevated and contribute to the destructive effects of ischemia. Significant defects have been demonstrated in the mitochondrial production of ATP, in the actinomyosin ATPase system consistent with a defect in the tropomyosin-troponin system, in the calcium release function of sarcoplasmic reticulum, and in the sodium potassium ATPase system during myocardial ischemia. It has been demonstrated that the presence of glucose prevents the large loss of certain critical amino acids from myocardium during hypoxia. Many of these new findings concerning the underlying mechanisms of myocardial cell injury and death due to ischemia have important implications and hold theoretical promise for the eventual development of interventions to counter the destructive effects of ischemia.

Polypeptide analogs of angiotensin have been synthesized and have been shown to stimulate mitochondrial ATP production and possess significant inotropic effects under hypoxic conditions with very little vasoconstrictor effects. In addition to the obvious therapeutic implications regarding increasing oxygen efficiency in the ischemic heart, these studies hold promise of significant new basic understanding of hormone effects on subcellular processes such as mitochondria and protein kinase.

During the coming year these contracts will continue to pursue their originally agreed upon scientific objectives. In addition, 44 proposals

in response to a new request for proposals on this topic have been received and are presently in the process of secondary review within the Institute.

Pennsylvania State University

Contract No. NIH-71-2499
Contract Amount: $197,879 (6/23/71 to 6/22/72)
Principal Investigator: Howard E. Morgan, M.D.

Certain critical subcellular mechanisms are being investigated during myocardial ischemia. A perfused working rat heart model has been developed which allows controlled degrees of myocardial ischemia. It has been found that in contrast to hypoxia, which increases glucose utilization in association with depletion of high energy phosphates, ischemia leads to loss of ATP and creatine phosphate without a compensatory increase in glucose utilization. Studies have demonstrated a 50% reduction of protein synthesis in hypoxic hearts due to restraints at the level of peptide chain elongation, which can be partially overcome by addition of insulin. Biochemical and electron micrographic evidence suggests that lysosomal activity may be markedly elevated and may contribute to the destructive effects of ischemia.

University of Pennsylvania

Contract No. NIH-71-2494
Contract Amount: $82,806 (6/7/71 to 6/6/72)
Principal Investigator: John R. Williamson, Ph.D.

The metabolism of certain amino acids which play a key intermediate role between glycolysis and mitchondrial ATP production are being studied in hypoxic and ischemic myocardium. It has been demonstrated that the presence of glucose prevents a large loss of aspartate and glutamine from the myocardial cell during hypoxia. Studies of calcium uptake and release by various subcellular compartments have demonstrated that hypoxia diminishes the occupancy of intracellular, rapid release sites for calcium.

Baylor College of Medicine

Contract No. NIH-71-2493
Contract Amount: $121,728 (6/25/71 to 6/24/72)
Principal Investigator: Arnold Schwartz, M.D.

Certain key biochemical functions are being studied during myocardial ischemia. A marked depression in mitochondrial respiratory control (ability to produce ATP) has been demonstrated during myocardial ischemia

which was correlated with calcium accumulating activity of mitochondria. A defect in the carnitine stimulated oxidation of palmitic acid has been shown to occur during myocardial ischemia which may represent an important defect in the transport of vital energy fuel into mitochondria. Actomyosin ATPase has been found to be significantly depressed during myocardial ischemia, probably due to a defect in the tropomyosin-troponin system. Studies investigating certain membrane systems have demonstrated defects in the release of calcium by sarcoplasmic reticulum and a significant depression of the sodium potassium ATPase system during myocardial ischemia.

University of Wisconsin

Contract No. NIH-71-2497
Contract Amount: $109,182 (6/11/71 to 6/10/72)
Principal Investigators: Theodore L. Goodfriend, M.D. (Univ. of Wisconsin)
David W. Allmann, Ph.D. (Univ. of Indiana)
John M. Stewart, Ph.D. (Univ. of Colorado)

The goal of this multi-institution contract is to synthesize and identify a polypeptide analog which maximizes the property of angiotensin to increase myocardial contractility under hypoxic conditions and minimizes the vasoconstrictor properties of angiotensin. Polypeptide analogs of angiotensin have been synthesized which separate these two properties, and two promising analogs with significant inotropic activity but virtually no vasoconstrictor effects have been synthesized.

Maine Medical Center

Contract No. NIH-71-2495
Contract Amount: $61,350 (6/22/71 to 6/21/72)
Principal Investigators: C.V. Nelson, Ph.D. (Maine Medical Center)
E.T. Angelakos, M.D., Ph.D. (Hahnemann Medical College)

The effect of locally released catecholamines in the ischemic and infarcted myocardium on ultimate size of infarction is being studied. Pharmacological blocking agents will be tested for their ability to protect ischemic myocardium and minimize infarct size. In addition, the integration method of surface potential measurement is being explored as a means of evaluating size and location of infarcts.

Boston University

Contract No. NIH-71-2498
Contract Amount: $57,982 (6/21/71 to 6/20/72)
Principal Investigator: William Hood, Jr., M.D.

The effects of four interventions (hypothermia, glucose-potassium-insulin infusion, free fatty acid infusion, and hyperbaric oxygenation) on ischemic, intermediate, and normal myocardium are being assessed by local mechanical performance acutely and ultimate infarct size.

PHYSIOLOGICAL AND BIOCHEMICAL PROCESSES FUNDAMENTAL TO NEW THERAPEUTIC METHODS - CONTROL OF LETHAL ARRHYTHMIAS

Since lethal arrhythmias account for a substantial fraction of sudden and even of late cardiac deaths, and since preventive and therapeutic methods for their control are inadequate, a new request for proposals on Control of Lethal Arrhythmias was distributed. The solicitation emphasized non-clinical studies focused upon fundamental processes and interventions which may ultimately lead to clinically applicable techniques, as well as upon clinical studies of approaches which are particularly promising and best suited for evaluation in the clinical setting. Thirty-two proposals were received and have been reviewed; the most promising are in the contract negotiation stage and awards in the current fiscal year are anticipated.

Annual Report Of
NATIONAL BLOOD RESOURCE PROGRAM
July 1, 1971 through June 30, 1972

Branch Summary

BACKGROUND: The National Blood Resource Program was established in FY 1967 with a 1.95 million dollar appropriation by Congress in the National Heart and Lung Institute budget. These funds were provided in response to a critical problem relative to the national supply of blood and blood components for transfusion. Specifically, the acquisition of scientific information regarding fractionation techniques resulted in an increasing identification of the cellular and protein components of blood as separately useful. However, there was at that time and there remains today a serious technological lag which prevents the large-scale application of this knowledge. This problem is made acute by the rapidly increasing civilian and military needs for blood components. It was determined that these critical demands could be met if component blood transfusion therapy was more extensively employed and if non-utilization of whole blood due to outdating in storage could be diminished. Consequently, early in the development of the Program, emphasis was on research and blood preservation and fractionation. Initial contracts were awarded in support of studies of adenine as a blood preservative. Much of the work in this area was completed during FY 1969.

In FY 1967 a major project was undertaken in the field of blood fractionation with the American National Red Cross. More recently research in methods of platelet preservation has been undertaken. In recognition of the need to utilize stored blood in a more intelligent and effective fashion four contracts in computerized automation of donor blood inventory and donor-recipient information systems were let in FY 1968. This work is near conclusion. Beginning in FY 1969 contracts were let to improve the effectiveness of detection of hepatitis in transfused blood in donors.

In FY 1971 the Blood Program underwent a large expansion in response to the pressing need for programmed research in blood banking and blood therapy. This expansion encompassed an enlargement of research in the detection and prevention of hepatitis transmission in blood and blood products, improved donor-recipient identification systems in blood transfusion, preparation of histocompatibility antigen-poor blood, and standardization of cryoprecipitate preparations. New program ideas included research in the prenatal diagnosis of inherited hematologic diseases, specifically hemophilia and sickle cell disease, and clinical trials in the therapy of sickle cell crisis. Finally, a systematic study of blood banking techniques and blood therapy in this country was initiated through a contract with a major management consultant firm. Staff of the National Blood Resource Branch have worked closely with members of the consultant firm in this effort.

In FY 1972, three major projects were undertaken in an effort to increase the safety of the national blood resource. These included research to determine the incidence of sequelae, and the mechanism of production,

of cytomegalovirus in transfused recipients; projects to elucidate the epidemiology and bio-immunology of human carriers of the hepatitis-associated antigen; and national trials to determine the efficacy in hepatitis prevention or treatment of gamma globulin containing a high titer of antibody to the hepatitis-associated antigen. These controlled double-blind trials should be completed by 1974.

2.1.1.1 Blood Procurement and Distribution Systems
A. Automated Donor Blood Inventory-Donor Blood Recipient Information System

In order to ascertain the efficacy of computers in promoting safety, proper distribtuion, and reduced waste of our national blood resource, the National Blood Resource Branch embarked upon a three year feasibility study in FY 1968. Funding for these projects essentially ended in September of 1971, and evaluation of the results of the study is underway.

Over the six months since NHLI funding was stopped, all four centers have remained viable with computers as an intimate part of their function. Tentative findings of the study may be summarized as follows. Computerization is most advantageous in large regional blood systems; however, cost-efficiency depends greatly upon the restrictions upon the blood bank as well as the services to be provided. Possible services include donor recruiting, donor group records and group control, blood inventory and forecasting, blood distribution, performance statistics and accounting. Savings from the use of computers arise principally from achievement of more effective management of blood collection and inventories, not from reduction in clerical costs. A computer cannot be substituted for organization and management to improve substantially the effectiveness and efficiency of a poorly run blood service system. The enormous experience gained in these projects should allow other blood centers to adopt computer methods to their needs at considerable reduction in required effort and expense. An in-depth overview of the NBRB computer feasibility study should be available to industry and the public by June 1972.

Community Blood Council of Greater New York PH 43-68-1403
New York, New York
Principal Investigator: Dr. Robert L. Hirsch
FY 1972 Support: -0- Previous funding: $757,416

Michael Reese Research Foundation NIH 69-57
Chicago, Illinois
Principal Investigator: Dr. Aaron M. Josephson
FY 1972 Support: -0- Previous funding: $783,880

Milwaukee Blood Center PH 43-68-1425
Milwaukee, Wisconsin
Principal Investigator: Dr. Richard Aster
FY 1972 Support: -0- Previous funding: $706,747

Research Foundation of State University of New York PH 43-68-1281
Buffalo, New York
Principal Investigator: Dr. Edward L. Wallace
FY 1972 Support: -0- Previous funding: $510,259

B. Operations Research Study of the American Blood System

Recognizing that many of the obstacles that impeded the provision for the American people of an adequate supply of safe high quality blood and blood components resided in management systems rather than in the technological area, the National Blood Resource Branch, with the help of its Advisory Committee, undertook a systematic study of blood banking in America. It soon became apparent that one of the problems was a lack of information or data on any parameter of this complex system. Therefore in FY 1971 the Branch contracted for the services of Booz, Allen and Hamilton to carry out a national study of the blood supply system. The ongoing study consists of two major parts: a) An overall description of the existing blood system including the role played by the pharmaceutical industry, the regulatory arrangements, the role of major organization such as Red Cross and the American Association of Blood Banks, and an in-depth study of the functioning of a sample of blood banks. b) A study of the problem of hemophilia care as an exemplar of the interaction of many of the problems facing the blood banking system. A related contract was awarded to the State University of New York at Buffalo to provide guidance and medical and scientific consultation to Booz, Allen and Hamilton and liaison with the National Blood Resource Branch. These two projects are now in an advanced state of fulfillment of their work and final extensive reports are expected in July 1972.

Booz-Allen Public Administration Service, Inc. NIH-71-2400
Washington, D.C.
Principal Investigator: Mr. Donald Cook
FY 1971 Support: $325,000 Previous funding: -0-

Research Foundation State University of New York NIH 71-2500
Buffalo, New York
Principal Investigator: Dr. Douglas Surgenor
FY 1971 Support: $146,845 Previous funding: -0-

2.1.1.2 Blood Supply
A. Studies on Oxygen Transport by Stored Blood (2,3 DPG)

When blood is stored prior to transfusion, it has been shown that red blood cell 2,3 Diphosphoglycerate levels decrease with a resulting shift of the hemoglobin-oxygen disassociation curve, such that oxygen is less available to the tissues. Thus, stored blood may be a less efficient transporter of oxygen than fresh blood. In fiscal year 1971 the National Blood Resource Program initiated a program to evaluate the significance of this physico-chemical change upon the recipient's ability to recover from a stressful situation which requires blood transfusion. The projects in this field are primarily designed to study the

physiologic effects of the transfusion of 2,3 diphosphoglycerate-poor blood in animals and man. In addition, means are being sought to prevent the loss of 2,3 Diphosphoglycerate from stored blood. To date it has been clearly demonstrated that transfusion of blood with decreased 2,3 Diphosphoglycerate produces an appreciable decrease in venous oxygen pressure in resting rats. During the coming year emphasis will be placed on human as well as animal studies.

Children's Hospital Medical Center NIH 71-2103
Boston, Massachusetts
Principal Investigator: Dr. Sherwin Kevy
FY 1972 Support: $31,874 Previous funding $45,670

Laboratory for Comparative Biochemistry NIH 71-2104
San Diego, California
Principal Investigator: Dr. Grant R. Bartlett
FY 1972 Support: $31,874 Previous funding: $22,390

King County Central Blood Bank NIH 71-2105
Seattle, Washington
Principal Investigator: Dr. Robert D. Woodson
FY 1972 Support: $78,787 Previous funding: $42,656

Washington University School of Medicine NIH 71-2106
St. Louis, Missouri
Principal Investigators: Dr. Harold S. Kaplan and Dr. John A. Collins
FY 1972 Support: $31,561 Previous funding $41,713

Ohio State University NIH 71-2107
Columbus, Ohio
Principal Investigator: Dr. Stanley Balcerzak
FY 1972 Support: $50,550 Previous funding: $78,338

2.1.1.3 Hemophilia and Component Therapy
A. Standardization of Cryoprecipitate

In fiscal year 1971 the National Blood Resource Program initiated studies to define a standard process for producing cryoprecipitated Factor VIII which would ensure the highest yield per unit of blood. Any laboratory or blood bank that applies this process with attention to the prescribed details would be able to produce packages of this material that are more uniform in potency and so may be employed clinically with greater confidence. Six studies have been supported in this area. During the first year of work much progress has been made. It is now clear that the yield of cryoprecipitate from a unit of blood is effected by (a) time of storage from phlebotomy to processing, (b) cryoprecipitate thawing time, (c) volume of solvent, (d) plastic composition of blood bag, (e) type of anticoagulant used, (f) post-exercise state of the donor, (g) degree of mixing of freshly drawn blood, and (h) harvesting of platelets. These parameters can be adjusted to give the highest yield of cryoprecipitated Factor VIII, the mainstay of treatment for hemophiliacs throughout the United States.

American National Red Cross NIH-71-2394
Washington, D.C.
Principal Investigator: D.C. Triantaphyllopoulos, M.D.
FY 1972 Support: -0- Previous funding: $24,383

Blood Research Institute, Inc. NIH-71-2395
Boston, Massachusetts
Principal Investigator: Marshall Melin, Ph.D.
FY 1972 Support: -0- Previous funding $78,570

Children's Hospital NIH-71-2396
Boston, Massachusetts
Principal Investigator: Sherwin Kevy, M.D.
FY 1972 Support: $18,409 Previous funding: $20,800

Thomas Jefferson University NIH-71-2397
Philadelphia, Pennsylvania
Principal Investigator: Edward R. Burka, M.D.
FY 1972 Support: $90,285 Previous funding: $94,900

King County Central Blood Bank NIH-71-2398
Seattle, Washington
Principal Investigator: Lawrence A. Harker, M.D.
FY 1972 Support: $64,115 Previous funding: $75,480

University of Southern California NIH-71-2399
Los Angeles, California
Principal Investigator: Carol Kasper, M.D.
FY 1972 Support: $42,693 Previous funding: $75,480

B. Platelet Preservation

The preservation of platelets for transfusion to thrombocytopenic patients is limited by platelet fragility and short life span. Platelets recovered from blood that has been stored at 4°C remain viable for only six hours and must be transfused within this time period. In fiscal year 1970 the National Blood Resource Program undertook support of studies to develop techniques to increase the in vivo lifespan of platelets. Four projects are now active in this area. Progress has been made since the initiation of these contracts. A method has been developed which permits storage of platelets for 72-96 hours without loss of clinical effectiveness. This storage time may be increased even more by chemical additives now being investigated. Of these Prostaglandin E_1 appears to be the most promising. Work is also underway to develop a platelet freezing technique which would allow storage of type specific platelets for perhaps a year or more without loss of clinical effectiveness. The extension of platelet storage time will ensure that an adequate number of platelets for treatment of thrombocytopenic patients will always be on hand in the nation's blood banks.

Milwaukee Blood Center, Inc. NIH-70-2213
Milwaukee, Wisconsin
Principal Investigator: Dr. Richard H. Aster
FY 1972 Support: $116,500 Previous funding: $233,450

King County Central Blood Bank NIH-70-2214
Seattle, Washington
Principal Investigator: Dr. Sherril Slichter
FY 1972 Support: $61,723 Previous funding: $112,820

Presbyterian University of Pennsylvania NIH-70-2212
Philadelphia, Pennsylvania
Principal Investigator: Dr. Frank H. Gardner
FY 1972 Support: -0- Previous funding: $118,000

The Memorial Hospital NIH-71-2252
Pawtucket, Rhode Island
Principal Investigator: Dr. Mario Baldini
FY 1972 Support: $55,610 Previous funding: $51,000

2.1.1.4 Safety of Blood Therapy
A. Hepatitis Program

1. Production and Distribution of Antibody to the Hepatitis-Associated Antigen (HB Ab) in Large Animals

During the second year of this sub-program area, the major goal was to produce high quality HB Ab (hepatitis B antibody) for research and educational purposes, as well as to supply this reagent in areas where it was not commercially available for routine blood donor testing. HB Ab is a necessary reagent for testing blood for HB Ag (hepatitis B antigen) a substance whose presence correlates highly with the transmission of hepatitis. Sheep, horses, monkeys and goats were successfully immunized, and large amounts of HB Ab produced. After these reagents were tested for potency and purity at the Massachusetts State Laboratories, they were bottled and labelled for distribution throughout the United States and abroad.

Demand for the reagents has been widespread. During fiscal year 1971-1972 one-third of all state health departments requested them in order to conduct training programs to teach technicians how to perform the necessary serological tests for HB Ag. In addition, materials were supplied to the U.S. military establishments abroad, to certain U.S. territories and to the American College of Pathologists for testing and educational purposes. Because a sufficient amount of hepatitis B antibody is now commercially available to supply the nation's needs, the National Blood Resource Branch plans to terminate this program, retaining the capacity to distribute the remaining reagents for educational and research purposes as needed.

Baylor College of Medicine NIH 70-2231
Houston, Texas
Principal Investigator: Dr. Joseph Melnick
Funding given in section 2. below.

Cordis Corporation NIH 70-2232
Miami, Florida
Principal Investigator: Dr. Seymour Halbert
Funding given in section 2. below.

Community Blood Council of Greater New York NIH 70-2236
New York, New York
Principal Investigator: Dr. Alfred Prince
Funding given in section 2. below.

New York State Department of Health NIH 70-2240
Albany, New York
Principal Investigator: Dr. James Pert
Funding given in section 2. below.

Harvard School of Public Health NIH 71-2064
Boston, Massachusetts
Principal Investigator: Dr. George Grady
FY 1972 Support: $42,905 Previous Funding: $31,895

2. Detection of Hepatitis in Blood

Ten studies were supported in an effort to develop a rapid, sensitive method to detect HB Ag (hepatitis B antigen), suitable for testing in blood banks. Without such techniques, only an estimated one-third of blood units infectious for hepatitis are detected by the conventional counter-electrophoresis (CEP). If it were possible to remove all units of blood that contained HB Ag, then the incidence of post-transfusion hepatitis would undoubtedly be significantly reduced. Investigations over the past year have concentrated on two different serological tests (HAI and RIA) which offer the best opportunity to greatly increase assay sensitivity; tentative conclusions include the following: a) The hemagglutination inhibition (HAI) technique, while capable of detecting 20% more positives than CEP, is not yet ready for routine use due to lack of knowledge concerning suitable reagents. This method appears to be less sensitive than radio-immuno assay. b) The radio-immuno assay (RIA) of the labeled antigen type is not at present recommended for routine blood bank use because of the incidence of false positives and the need to determine its efficiency, through prospective clinical trials in reducing the incidence of post-transfusion hepatitis. c) Radio-immuno assays of the labeled-antibody type appear to be the best of the available techniques for the detection of human blood carriers of HB Ag. At present, however, this method is too slow for satisfactory utilization by large blood banks.

The National Blood Resource Branch plans to continue support in this area. Emphasis is to be placed upon the refinement of a rapid labeled-antibody, solid phase radio-immuno assay procedure, maintaining a high level of sensitivity and specificity, as well as being HB Ag subtype specific.

New York State Department of Health NIH-2240
Albany, New York
Principal Investigator: Dr. James Pert
FY 1972 Support: -0- Previous funding: $80,787

Institute for Cancer Research NIH 70-2234
Philadelphia, Pennsylvania
Principal Investigator: Dr. Baruch Blumberg
FY 1972 Support: $708,000 Previous funding: $175,800

Baylor College of Medicine NIH 70-2231
Houston, Texas
Principal Investigator: Dr. Joseph Melnick
FY 1972 Support: $183,500 Previous funding: $335,131

Cordis Corporation NIH 70-2232
Miami, Florida
Principal Investigator: Dr. Seymour Halbert
FY 1972 Support: -0- Previous funding: $181,547

Community Blood Council of Greater New York NIH 70-2236
New York, New York
Principal Investigator: Dr. Alfred Prince
FY 1972 Support: $82,880 Previous funding: $351,658

University of California Medical Center NIH 71-2355
San Francisco, California
Principal Investigator: Dr. Girish N. Vyas
FY 1972 Support: $142,620 Previous funding: $65,212

University of California at Los Angeles NIH 71-2351
Los Angeles, California
Principal Investigator: Dr. Gary Gitnick
FY 1972 Support: $59,453 Previous funding: $19,359

Washington University NIH 71-2353
St. Louis, Missouri
Principal Investigator: Dr. Richard Aach
FY 1972 Support: $90,990 Previous funding: $60,092

Aerojet Medical & Biological System NIH 71-2350
El Monte, California
Principal Investigator: Dr. A. F. Wells
FY 1972 Support: $70,000 Previous funding: $45,591

Syracuse University NIH 71-2352
Syracuse, New York
Principal Investigator: Dr. James E. Smith
FY 1972 Support: -0- Previous funding: $25,415

3. Removal/Inactivation of the Agent of Hepatitis from Blood and Blood Products

Because testing for HB Ag (Hepatitis B antigen) does not eliminate all units of blood infectious for the agent causative of hepatitis, this program area was begun in June of 1971 to develop techniques to remove or inactivate that agent. Should it be possible to efficiently and inexpensively remove the virus from blood without damage to cellular or protein components, the safety of the national blood resource would be significantly increased. Three approaches are being studied at this time: a) A double-blind controlled trial to test the efficacy of washed red cells in reducing the incidence of post-transfusion hepatitis has been initiated and is underway. The trial will not reach statistical significance until about December 1973. b) Various formulations of polyelectrolytes have been studied for their ability to selectively remove HB Ag from blood; PE-52 was selected and has been impregnated into a suitable fiber for clinical testing. c) Polyethylene glycol to fractionate blood into hepatitis-free components is also being studied. High yields of blood clotting factors II and VIII have been obtained, free from HB Ag by conventional methods (counter-electrophoresis). d) Automated equipment to produce hepatitis-free fibrinogen has been developed; fibrinogen so produced is scheduled for testing in chimpanzees for its hepatitis safety. The National Blood Resource Program plans continued support to the three projects which offer the most promise for a practical method of virus removal.

Baylor College of Medicine NIH 71-2354
Houston, Texas
Principal Investigator: Dr. Joseph Melnick
FY 1972 Support: -0- Previous funding: $48,685

New York University Medical Center NIH 71-2359
New York, New York
Principal Investigator: Dr. Alan Johnson
FY 1972 Support: $73,808 Previous funding: $58,333

New York State Department of Health NIH 71-2357
Albany, New York
Principal Investigator: Dr. James Pert
FY 1972 Support: -0- Previous funding $50,923

Blood Research Institute NIH 71-2356
Boston, Massachusetts
Principal Investigator: Dr. John Hinman
FY 1972 Support: $184,868 Previous funding: $152,713

Community Blood Council of Greater New York NIH 71-2358
New York, New York
Principal Investigator: Dr. Alfred Prince
FY 1972 Support: $69,966 Previous funding: $59,589

4. Epidemiology and Bio-immunology of HB Ag Carriers

With the advent of routine screening of blood for hepatitis B antigen, over 10,000 human carriers are expected to be detected each year. While the use of blood from such carriers is known to be highly correlated with post-transfusion hepatitis, the frequency of non-parenteral spread, as well as the associated morbidity of such individuals is unknown. Investigations into the epidemiology and bio-immunology of HAA carriers have important implications for blood banking: improved means for the detection of the HAA carrier state, as well as for individuals capable of becoming carriers; methods of terminating the carrier state, reducing their threat to blood recipients and associates; knowledge of the immunologic status of the HAA carrier as well as the liability of HAA transmission by various routes; guidelines for health workers who are HAA carriers. In fiscal year 1972 the National Blood Resource Program awarded contracts in this area to the following investigators:

The New York Blood Center
New York, New York
Principal Investigator: Dr. Alfred Prince
FY 1972 Support: $300,000 Previous funding: -0-

Baylor College of Medicine
Houston, Texas
Principal Investigator: Dr. Joseph Melnick
FY 1972 Support: $70,000 Previous funding: -0-

Louisiana State University
Costa Rica
Principal Investigator: Dr. Victor Villarejos
FY 1972 Support: $99,860 Previous funding: -0-

University of California at San Francisco
San Francisco, California
Principal Investigator: Dr. Girish Vyas
FY 1972 Support: $120,000 Previous funding: -0-

5. Clinical Trials of Hyper-immune Gamma Globulin for Prophylaxis and Treatment of Acute Hepatitis B

The discovery of the hepatitis-associated antigen and the host of virological, biochemical, and immunological observations which have followed it, have made the field of hepatitis research one of the most rapidly advancing in medicine. Nevertheless, for the estimated yearly U.S. total of 30,000 overt cases of hepatitis, 1,500 hepatitis-related deaths, and thousands of asymptomatic carriers, recent advancements have

not been impressive in the treatment or prophylaxis of the serum (MS 2) variety. In fiscal year 1972, the National Blood Resource Program undertook the support of nation-wide, controlled, double-blind clinical trials to determine the efficacy of gamma globulin containing a high titer of hepatitis B antibody (HB Ab) in the following populations: hospital personnel who were accidentally parenterally exposed to HB Ag-positive material; renal dialysis patients and staff in particularly hepatitis prone centers; patients with acute fulminant hepatitis; and cardiovascular surgery patients receiving large-volume transfusions. The growing impression among medical and lay people that high-titer gamma globulin is beneficial must be submitted to a randomized double-blind trial early, before this promising but unproven therapy becomes widespread. Awards were made to the following institutions to coordinate the clinical trials:

Tufts University School of Medicine
Boston, Massachusetts
Principal Investigator: Dr. George F. Grady
FY 1972 Support: $287,515 Previous funding: -0-

University of Southern California
Los Angeles, California
Principal Investigator: Dr. James Mosley
FY 1972 Support: $371,180 Previous funding: -0-

The New York Blood Center
New York, New York
Principal Investigator: Dr. Alfred Prince
FY 1972 Support $300,077 Previous funding: -0-

Walter Reed Institute of Medical Research
Washington, D.C.
Principal Investigator: Dr. Marcel Conrad
FY 1972 Support: $20,000 Previous funding: -0-

B. Epidemiology and Development of Detection Systems for Cytomegalovirus as Transmitted by Blood Transfusion

Since 1956 when human cytomegaloviruses were first isolated, a conception has emerged of a ubiquitous agent, with protean manifestations, from which few men escape infection during their lifetime. More recently, transfused blood has been implicated as the transmission medium for serious disease, sometimes fatal, resulting from CMV. However, the data at present are inconclusive as to whether CMV infection results from transmission by transfused blood, or by activation of latent virus in the recipient, secondary to stimulation by foreign white cells, drugs, the stress of surgery, or other causes. Also, presently available detection systems may not be adequate for definitively resolving this dilemma. The cost to society is significant. While CMV infection in the post-operative heart-lung bypass patient is usually self-limited, episodes of pancreatitis, hepatitis, hemolytic anemia, and immunological abnormalities have been reported. The transfused patient who is immunosuppressed does less well; up to 50% who survive for one or two months

after transplantation have evidence of active CMV infection. Should blood be conclusively proven as the mode of transmission, a method to detect infectious blood, applicable to mass screening, would be needed to reduce the morbidity and mortality associated with CMV. In fiscal year 1972, the National Blood Resource Program began support of six projects which would define the role of transfusion in the production of CMV infection among recipients of blood or blood components, and would determine the magnitude and extent of this disease in high risk populations.

University of North Carolina
Chapel Hill, North Carolina
Principal Investigator: Dr. Joseph Pagano
FY 1972 Support: $70,102 Previous funding: -0-

Community Blood Center of Greater Kansas City
Kansas City, Missouri
Principal Investigator: Dr. William Bayer
FY 1972 Support: $101,320 Previous funding: -0-

University of Pittsburgh
Pittsburgh, Pennsylvania
Principal Investigator: Dr. Monto Ho
FY 1972 Support: $66,852 Previous funding -0-

Case-Western Reserve University
Cleveland, Ohio
Principal Investigator: Dr. Eli Gold
FY 1972 Support: $86,950 Previous funding: -0-

L.A. County-Harbor General Hospital
Los Angeles, California
Principal Investigator. Dr. Milan Fiala
FY 1972 Support: $60,000 Previous funding: -0-

Duke University Medical Center
Durham, North Carolina
Principal Investigator: Dr. David Lang
FY 1972 Support: $55,454 Previous funding: -0-

C. The Removal of Histocompatibility Antigens from Blood

Patients who receive transplanted organs, especially kidneys, often require blood transfusion prior to the transplantation. When these patients are transfused they may become sensitized to the white cell and platelet histocompatibility antigens present in whole blood. If this occurs, the incidence of rejection of the transplanted organ is much higher than if the patient has not received blood transfusions. Since many of these patients are anemic and must be transfused, it is desirable to remove as many white cells and platelets as possible from the blood before transfusion thus reducing the incidence of sensitization and early rejection. The research sponsored by the National Blood Resource Program is aimed at evaluating processes for removing white cells from blood. There are four

contracts in the area (see list below). The work was begun in fiscal year 1971. To date the degree of white cell and platelet removal afforded by various available techniques has been evaluated. During fiscal year 1972 there will be an effort to develop a more efficient white cell removal process than any presently available and to initiate clinical studies to investigate the frequency of sensitization to histocompatibility antigens in patients transfused with blood rendered white cell poor by one of the available processes.

American National Red Cross NIH 71-2407
Washington, D.C.
Principal Investigator: Dr. Harold Meryman
FY 1972 Support: $97,727 Previous funding: $113,337

Irwin Memorial Blood Bank NIH 71-2408
San Francisco, California
Principal Investigator: Dr. Herbert Perkins
FY 1972 Support: $66,004 Previous funding: $65,166

University of Kentucky NIH 71-2409
Lexington, Kentucky
Principal Investigator: Dr. William Miller
FY 1972 Support: $45,334 Previous funding: $47,300

Minneapolis War Memorial Blood Bank NIH 71-2410
Minneapolis, Minnesota
Principal Investigator: Dr. Herbert Polesky
FY 1972 Support: $45,678 Previous funding: $51,372

D. Donor-Recipient Identification in Blood Transfusion

In spite of the fact that blood is carefully screened, tested, and managed under carefully written standards from the time of donation, morbidity and mortality occur each year from transfusion reactions, due to human error. To reduce these hazards, the National Blood Resource Branch in June of 1971 initiated studies to develop systems, not requiring human judgment and accuracy, and capable of performing almost all labeling and patient identification procedures from donor to recipient, to be eventually tested on a pilot scale in a clinical setting.

In the first nine months of the project, three groups of investigators designed and built devices necessary to label objects and to check the identity of those labels in a foolproof way. Labeling mechanisms being studied include embossed cards, magnetic tape and a perforated material on tube heads. Devices to identify machine-readable codes have been developed and are being tested. While these systems will satisfactorily foolproof most areas subject to human error in the present manual system for handling blood, none would eliminate error by the technician at cross-match where human manipulation is at present necessary. In fiscal year 1972 all three systems will be used in hospitals, and indicated modification implemented.

Medical Laboratory Automation, Inc.
Mt. Vernon, New York
Principal Investigator: Mr. John J. Hartnett
FY 1972 Support: $200,000 (est.) Previous funding: $142,040

Georgetown University
Washington, D.C.
Principal Investigator: Martin Rubin, Ph.D.
FY 1972 Support: $140,000 (est.) Previous funding: $122,242

University of California Medical Center
San Francisco, California
Principal Investigator: Dr. George Brecher
FY 1972 Support: $66,000 (est.) Previous funding $55,500

2.1.1.5 Thrombotic Diseases
A. Urokinase Streptokinase Pulmonary Embolism Trial

The first phase of this major cooperative trial was completed in August 1970. Seventy-eight patients were randomized to heparin therapy and 82 to urokinase therapy followed by heparin. The trial was designed to measure primarily the thrombolytic capacity and possible therapeutic benefits of urokinase. The urokinase and subsequent heparin regimen significantly accelerated clot resolution as evidenced by angiograms, photoscans, and hemodynamic measurements. Principal results have been published:

1. The Urokinase Pulmonary Embolism Trial Study Group, "Urokinase Pulmonary Embolism Trial Phase I Results" JAMA-214 pp 2163-72, 1970.

2. The Pulmonary Embolism Trial Study Group, "Urokinase in the Treatment of Pulmonary Embolism," THROMBOSIS ET DIATHESIS HAEMORRHAGICA (accepted for publication).

3. Hyers, T.M., Stengle, J.M., Sherry, S. - "Treatment of Pulmonary Embolism with Urokinase - Results of Clinical Trial (Phase 1)," CIRCULATION (Editorial) -42 pp 979-980, 1970.

Upon completion of the first phase of the trial, a second phase was entered in which patients received a 12 or 24 hour thrombolytic regimen, soon after suffering pulmonary embolism. All patients receive subsequent heparin. One hundred and thirty patients have been treated as of April 19, 1972. This study will compare the thrombolytic capacity and toxicity of the two most common thrombolytic agents, streptokinase and urokinase. Results of the second phase of the trial will be published in 1973 after the trial is completed. The participating institutions in the current trial are:

Boston City Hospital NIH 70-2297
Boston, Massachusetts
Principal Investigator: Joseph V. Messer, M.D.
FY 1972 Support: -0- Previous funding $110,740

University of Colorado Medical Center PH 43-68-1385
Denver Colorado
Principal Investigator: Edward Genton, M.D.
FY 1972 Support: -0- Previous funding: $74,980

Emory University School of Medicine NIH 69-2120
Atlanta, Georgia
Principal Investigator: Nanette K. Wenger, M.D.
FY 1972 Support: $72,815 Previous funding: $152,425

Johns Hopkins University PH 43-68-1398
Baltimore, Maryland
Principal Investigator: William Bell, M.D.
FY 1972 Support: $60,000 Previous funding: $180,800

Marshfield Clinic Foundation for Medical Research and Education PH 43-68-1399
Marshfield, Wisconsin
Principal Investigator: Richard D. Sautter, M.D.
FY 1972 Support: $69,408 Previous funding: $140,170

University of Michigan NIH 69-2121
Ann Arbor, Michigan
Principal Investigator: Park W. Willis, III, M.D.
FY 1972 Support: -0- Previous funding: $114,480

University of Texas Medical Branch NIH 69-2124
Galveston, Texas
Principal Investigator: William deGroot, M.D.
FY 1972 Support: -0- Previous funding: $132,411

University of Washington PH-43-68-1429
Seattle, Washington
Principal Investigator: J.R. Blackmon, M.D.
FY 1972 Support: $75,000 Previous funding: $273,282

B. Clinical Trials of Thrombolytic Agents in Acute Myocardial Infarction

Recognizing the importance of congestive heart failure and cardiogenic shock as contributors to mortality from acute myocardial infarction, the National Blood Resource Branch has a continuing interest in the possible role of thrombolytic agents in salvaging ischemic myocardial tissue in acute myocardial infarction. Pilot studies in this area funded under RFP NHLI-71-13 have yielded an excellent protocol for use in an expanded clinical trial. Eight institutions were involved in these pilot studies and are listed below. Results from these pilot studies, along with data emerging from European trials, has encouraged NHLI to proceed with issuance of a new RFP inviting praticpation in a controlled trial of thrombolytic agents in the treatment of acute myocardial infarction. The present pilot studies will be phased out by October 1972, by which time the expanded, definitive trial is scheduled to begin.

Marshfield Clinic
Marshfield, Wisconsin
Principal Investigator: Dr. Richard Sautter
FY 1972 Support: -0- Previous funding: $57,800

University of Michigan
Ann Arbor, Michigan
Principal Investigator: Dr. Park W. Willis, III
FY 1972 Support: -0- Previous funding: $62,200

George Washington University
Washington, D.C.
Principal Investigator: Dr. George A. Kelser, Jr.
FY 1972 Support: -0- Previous funding: $62,437

Temple University
Philadelphia, Pennsylvania
Principal Investigator: Dr. James F. Spann, Jr.
FY 1972 Support: -0- Previous funding $77,100

University of Colorado
Denver, Colorado
Principal Investigator: Dr. Edward Genton
FY 1972 Support: -0- Previous funding: $35,618

Boston City Hospital
Boston, Massachusetts
Principal Investigator: Dr. Joseph V. Messer
FY 1972 Support: -0- Previous funding: $41,347

University of Texas
Galveston, Texas
Principal Investigator: Dr. Daniel C. Allensworth
FY 1972 Support: -0- Previous funding: $38,350

Veterans Administration Hospital
Durham, North Carolina
Principal Investigator: Dr. Abe Walston
FY 1972 Support: $66,480 Previous funding: -0-

C. Non-Urinary Urokinase

Encouraged by the experience in the Urokinase Pulmonary Embolism Trial, The National Blood Resource Program undertook the support of studies to explore the possibility of obtaining urokinase from non-urinary sources which would ensure the availability of an enlarged inexpensive supply of urokinase for exploration of the drug's efficacy in thromboembolic diseases. To date urokinase-producing cell cultures have been established. During the coming fiscal year the urokinase harvested from these cultures will be purified and tested to ensure a clinically safe and useful product.

Abbott Laboratories NIH-71-2405
North Chicago, Illinois
Principal Investigator: G. H. Barlow
FY 1972 Support: $227,172 (est.) Previous funding: $206,468

Collaborative Research, Inc. NIH-71-2406
Waltham, Massachusetts
Principal Investigator: Orrie M. Friedman, M.D.
FY 1972 Support: $149,475 (est.) Previous funding: $137,220

2.1.1.6 Sickle Cell Studies

A. Clinical Trials of Therapeutic Approaches to Sickle Cell Crisis

In spite of the degree of refined molecular knowledge about sickle cell hemoglobin, little is known about the pathophysiological mechanisms involved in precipitating and sustaining the painful vaso-occlusive crisis of sickle cell disease; and no treatment of proved efficacy is yet available for crisis. In fiscal year 1972 the National Blood Resource Branch initiated collaborative clinical trials of therapy for sickle cell vaso-occlusive crisis. The Southeastern Task Force has been investigating the efficacy of low dose urea therapy as compared to alkalinization, hydration, and electrolyte therapy. These intravenous therapies have all been tolerated well with no evidence of adverse effects. Approximately 47 patients have been treated in this randomized, modified double-blind clinical trial to date. Depending upon results of the present trials, a decision will be made whether or not to proceed with low dose urea therapy, or to increase its dosage. The Travenol Laboratories' cooperative group is comparing the efficacy of high dose urea therapy with hydration and electrolyte therapy. Approximately 45 patients have been treated according to protocol to date, with no significant adverse effects due to therapy. The protocol used in Travenol Laboratories' group is identical with that of the Southeastern Task Force as regards criteria of admission, criteria of exclusion, and criteria of response. The first data analysis session for the Travenol cooperative, controlled, modified double-blind trial is planned for June 1972. The Meharry Medical College clinical trial is a controlled, modified, double-blind, randomized trial comparing intravenous alkalinization versus hydration and electrolyte therapy. Approximately 12 patients have been treated to date according to protocol, with no significant adverse effects due to therapy reported by the investigators. The first data analysis session for evaluating the Meharry Study is planned by July 1972. The National Blood Resource Branch plans to continue each of these clinical trials for an additional year anticipating the achievement of significant results enabling termination of the trials by July 1973.

University of Tennessee
Knoxville, Tennessee
Principal Investigator: Dr. Alfred Kraus
FY 1972 Support: $145,213 Previous funding: $145,697

Bowman Gray School of Medicine
Winston-Salem, North Carolina
Principal Investigator: Dr. Robert Cooper
FY 1972 Support: $47,360 Previous funding: $40,068

Emory University
Atlanta, Georgia
Principal Investigator: Dr. B.R. Gendel
FY 1972 Support: $33,897 Previous funding: $33,506

Duke University
Durham, North Carolina
Principal Investigator: Dr. Wendell Rosse
FY 1972 Support: $38,688 Previous funding: $41,846

Travenol Laboratories, Inc.
Morton Grove, Illinois
Principal Investigator: Dr. Thomas A. Garrett
FY 1972 Support: $185,000 Previous funding: $179,028

Rockefeller Universtiy
New York, New York
Principal Investigator:
FY 1972 Support: $85,000 Previous funding: $61,600 (O.D.)

Meharry Medical College
Memphis, Tennessee
Principal Investigator: Dr. Robert S. Rhodes
FY 1972 Support: $100,000 Previous funding: $99,385

B. Studies in Sickle Cell Disease

Since the observation by Dr. J.B. Herrick of the peculiar sickle-shaped erythrocytes in the blood smear in an anemic West Indian Negro student, a great deal of biochemical information has accumulated on sickle cell disease. In spite of the degree of refined molecular knowledge about hemoglobin S, little is known about the pathophysiological mechanisms involved in precipitating the sickling event. Likewise, little is known about the cell energetics, transport kinetics, and membrane lipid metabolism of the sickle cell disease red blood cell under various conditions.

The National Heart and Lung Institute continues to have as one of its objectives the study of mechanisms for prevention and treatment of sickle cell disease. In fiscal year 1972, the National Blood Resource Branch undertook the support of 22 studies which would investigate the following issues:

1. What are the properties of sickle hemoglobin and of sickle hemoglobin-containing erythrocytes, which may be involved in the sickling process, and what mechanisms are effective in preventing and/or reversing sickling?

2. What are the biochemical and physiological characteristics of the irreversibly sickled, the reversibly sickled and the non-sickled erythrocyte from the homozygous S patient and what do modifications of the hemoglobin molecule do to these characteristics (e.g., cell energetics, transport kinetics, and membrane lipid metabolism)?
3. How do these cells function outside the patient (in vitro or in an animal model) in terms of flow characteristics, survival and oxygen delivery?
4. How do these cells function in the patient in terms of flow characteristics (e.g., conjunctival flow studies, thermography, washout studies, and scans), survival, and oxygen delivery, (e.g., Hickam-Frayser technique for measuring flow and 0_2 consumption in the retina)?
5. Can tissue damage and/or destruction and its progression over time be measured (e.g., by use of radioactive scans, enzyme studies, etc.) in the sickle cell disease patient?
6. Is there derangement of the coagulation-fibrinolytic system in the sickle cell disease patient, both in and out of crisis?
7. Is there derangment of the white blood cell or other component in the immune mechanism in the sickle cell disease patient?

Investigators supported in this research area are as follows:

Albert Einstein College of Medicine
New York, New York
Principal Investigator: Dr. Ronald L. Nagel
FY 1972 Support: $81,377 Previous funding: -0-

University of California, Davis
Davis, California
Principal Investigator: Charles F. Abildgaard, M.D.
FY 1972 Support: $43,300 Previous funding: -0-

Children's Hospital Medical Center
Boston, Massachusetts
Principal Investigator: David G. Nathan, M.D.
FY 1972 Support: $97,000 Previous funding: -0-

The Children's Hospital Research Foundation
Cincinnati, Ohio
Principal Investigator: C. Thomas Kisker, M.D.
FY 1972 Support: $26,000 Previous funding: -0-

George Washington University
Washington, D.C.
Principal Investigator: Wallace N. Jensen, M.D.
FY 1972 Support: $335,627 Previous funding: -0-

IIT Research Institute
Chicago, Illinois
Principal Investigator: Clare C. Johnston
FY 1972 Support: $40,000 Previous funding: -0-

University of Illinois Eye and Ear Infirmary
Chicago, Illinois
Principal Investigator: Dr. Morton F. Goldberg
FY 1972 Support: $61,000 Previous funding: -0-

Johns Hopkins Universtiy
Baltimore, Maryland
Principal Investigator: Dr. Samuel Charache
FY 1972 Support: $72,000 Previous funding: -0-

University of Kansas Medical Center
Kansas City, Kansas
Principal Investigator: Dr. Dennis A. Diederich
FY 1972 Support: $38,253 Previous funding: -0-

Milwaukee Blood Center, Inc.
Milwaukee, Wisconsin
Principal Investigator: Glenn E. Rodey, M.D.
FY 1972 Support: $27,000 Previous funding: -0-

Mount Sinai School of Medicine
New York, New York
Principal Investigator: Dr. Ralph Zalusky
FY 1972 Support: $41,345 Previous funding: -0-

The Ohio State University Research Foundation
Columbus, Ohio
Principal Investigator: Stanley P. Balcerzak, M.D.
FY 1972 Support: $104,000 Previous funding: -0-

University of Oklahoma School of Medicine
Oklahoma City, Oklahoma
Principal Investigator: Paul D. Stein, M.D.
FY 1972 Support: $46,526 Previous funding: -0-

Papanicolaou Cancer Research Institute
Miami, Florida
Principal Investigator: Dr. Bruce F. Cameron
FY 1972 Support: $60,000 Previous funding: -0-

St. Luke's Hospital Center
New York, New York
Principal Investigator: John F. Bertles, M.D.
FY 1972 Support: $97,600 Previous funding: -0-

Stanford University
Stanford, California
Principal Investigator: Dr. Linus Pauling
FY 1972 Support: $80,000 Previous funding: -0-

University of Tennessee
Memphis, Tennessee
Principal Investigator: Dr. Lorraine M. Kraus
FY 1972 Support: $97,000 Previous funding: -0-

University of Texas Medical Branch
Galveston, Texas
Principal Investigator: Mason Guest, M.D.
FY 1972 Support: $33,160 Previous funding: -0-

University of Texas Southwestern Medical School
Dallas, Texas
Principal Investigators: Dr. Michael Waterman & Dr. G. Larry Cottam
FY 1972 Support: $75,000 Previous funding: -0-

Washington University of St. Louis
St. Louis, Missouri
Principal Investigators: Dr. Harold Zarkowsky & Dr. Robert Hochmuth
FY 1972 Support: $65,000 Previous funding: -0-

Wayne State University School of Medicine
Detroit, Michigan
Principal Investigator: Dr. Ananda Prasaed
FY 1972 Support: $81,104 Previous funding: -0-

Yale University
New Haven, Connecticut
Principal Investigator: Howard A. Pearson, M.D.
FY 1972 Support: $45,210 Previous funding: -0-

C. Prenatal Diagnosis of Inherited Hematologic Diseases

The increasing sophistication of amniocentesis in the abnormal and normal pregnancy for diagnostic purposes has made feasible programmed research in the prenatal diagnosis of inherited diseases. Hemophilia and sickle cell disease have been chosen for the prime focus because these diseases are of concern to the blood program and exert a disproportionate demand on the Nation's blood and medical resources. Four projects in this area were begun in fiscal year 1971. Both direct and indirect (genetic linkage) approaches were investigated. Initial studies dealt principally with the prenatal diagnosis of sickle cell disease since it appears more likely that significant results will be obtained quicker here. To date excellent progress has been made toward the production of goat antiserum specific for hemoglobin S. Also the synthesis of Beta globin chains has been unequivocally demonstrated in reticulocytes of the midtrimester human fetus. Genetic linkage studies are proceeding well and within the next fiscal year a safe means of in utero fetal visualization should be perfected.

Johns Hopkins University School of Medicine NIH-71-2401
Baltimore, Maryland
Principal Investigators: H.S. Kazazian, M.D. & Michael M. Kaback, M.D.
FY 1972 Support: $31,644 Previous funding: $31,644

University of Rochester NIH-71-2402
Rochester, New York
Principal Investigators: Richard A. Doherty, M.D. & Peter T. Rowley, M.D.
FY 1972 Support: $65,728 Previous funding: $65,728

Johns Hopkins University School of Medicine NIH-71-2403
Baltimore, Maryland
Principal Investigators: Samuel H. Boyer, M.D. & Victor A. McKusick, M.D.
FY 1972 Support: $32,182 Previous funding: $38,457

University of Rochester NIH-71-2404
Rochester, New York
Principal Investigator: Lowell R. Weitkamp, M.D.
FY 1972 Support: $63,150 Previous funding: $63,150

ANNUAL REPORT OF
THE LIPID METABOLISM BRANCH

July 1, 1971 through June 30, 1972

BRANCH SUMMARY

The Lipid Metabolism Branch was established in FY '71 because it was felt that this was an opportune time for capitalizing on recent advances in the understanding of hyperlipidemia, especially through the use of the theoretical and practical concepts of hyperlipoproteinemia.

The Branch has the responsibility for planning, conducting, and directing a collaborative program of research into the structure, metabolism, and function of lipids and lipoproteins as they relate to atherosclerosis. It supports and coordinates a national research program designed to increase knowledge related to the etiology, diagnosis, and management of lipid disorders, especially those associated with premature vascular diseases.

To achieve these goals, the Branch established six Lipid Research Clinics (LRC's) and a Central Patient Registry (CPR) by the contract mechanism in June 1971. This Lipid Research Clinics Program supplements current research by providing support for a broad collaborative clinical study directly related to improving the diagnosis and management of hyperlipoproteinemia. The Lipid Research Clinics program serves the Branch's long-term goals by: 1) providing basic population laboratories, 2) evaluating and standardizing basic lipid and lipoprotein techniques and terminology, 3) determining the prevalence of lipid transport disorders, their causes and treatment and the effect of this treatment on premature atherosclerosis, 4) adhering to common protocols and methodology, common standardization programs, providing comparable patient populations, long-term observation and central collection, editing and monitoring of data.

The Central Patient Registry and the six Lipid Research Clinics have now been operational for almost one year. During this time, a functional inter-clinic organizational structure has emerged and led to an extensive two-volume Reference Manual of Operations for the Lipid Research Clinics governing all their collaborative activities. Several basic systems for the determination of cholesterol and triglyceride have been evaluated. Modification of one of these systems (Autoanalyzer II) by the Lipid Research Clinics shows great promise as a high volume reference method.

A detailed system for Quality Control and Standardization of basic methodology is operational. Prevalence studies have all been reviewed and modified by an ad hoc panel of experts; many clinics have completed field trials. The clinics have all agreed on a standardized submaximal exercise test to evaluate for ischemic heart disease. Standard forms for all phases of all prevalence studies have been completed and approved by the Lipid Research Clinic Directorate and the Office of Management and Budget. Finally, a skeleton protocol for a double blinded primary prevention trial employing diet and drug has received unanimous endorsement by the Lipid Research Clinics.

This year RFP-NHLI-72-1 was released by the Program Office in an effort to complete the network of regional Lipid Research Clinics, provide an ample sampling frame for prevalence studies and recruit additional patients for the proposed intervention trial (an estimated 3,600/4,000 Type II patients). Extensive review of 30 proposals received in response to this RFP has been completed and negotiations are now in progress for the establishment of six additional Lipid Research Clinics.

The Clinical Chemistry and Hematology Branch of the Center for Disease Control, Atlanta, Georgia, plays a vital role in the Lipid Research Clinics Program by serving as a lipid standardization laboratory. Their role is to coordinate and monitor the laboratory aspects of the study and provide the materials to insure standardization of methodology in each clinic. This Lipid Standardization Laboratory, and the Central Patient Registry, are responsible for all quality control procedures.

The internal operations of the Branch include the direction and administration of ongoing contracts, the development of requests for proposals and the review of proposals, the planning and integration of the overall Program, participation in research, and routine administration. In the direction and administration of contracts, emphasis is placed upon scientific excellence and Program relevance, upon the development of people and resources, and upon the fulfillment of Program goals. There is recognition of the need for flexibility in the scientific content and in the operation of the projects--within the bounds of Program structure and priorities and of the need for sound administrative and fiscal practices.

As in all branches of the collaborative program, primary technical review of all proposals is by experts predominantly from the extramural scientific community; their recommendations are considered in light of the additional study of the proposals by Program staff and in the context of Program needs; Program Office recommendations are further considered by reviewers advisory to the Director, NHLI, before contact is made with potential contractors. Scientific discussions between Program staff and potential contractors precede formal contract negotiations.

In the coming year, the Lipid Metabolism Branch will continue to develop along directions previously outlined. The Lipid Research Clinic network will have been completed and every effort will be made to have the core laboratories of the new Lipid Research Clinics operational as quickly as possible. Prevalence studies will commence at all the clinics employing standard forms and exercise tolerance testing. All clinics will have been standardized in terms of basic techniques and terminology and will be encouraged to collaborate in new method development and nutritional counseling, evaluation, and monitoring.

A major objective of this coming year is the completion of the planning and design for the common multicentric intervention trial to test the lipid hypothesis. A tentative timetable calls for completion of the protocol and design by November, the forms by the Spring, and the actual commencement of patient accrual by June 1, 1973.

It is hoped that the Lipid Metabolism Branch's Experimental Studies subprogram area will finally receive funding so that we will be able to support basic research into the structure, metabolism, and function of lipoproteins as they relate to atherosclerosis. The Branch hopes to be able to fund two specific areas in FY '73 by RFP. These are: 1) the search for and development of animal models of dyslipoproteinemias, 2) the development of improved methodology for assaying cholesterol absorption. The former is necessary if we are to explore the basic mechanisms underlying human disorders, the latter if we are to understand individual susceptibility to dietary cholesterol.

LIPID RESEARCH CLINICS

This subprogram supplements and extends current research efforts by providing support for a broad collaborative clinical study directly related to improving the diagnosis and management of hyperlipoproteinemia, determining its prevalence and establishing further opportunities for research into its causes and treatment and the effect of this treatment on premature atherosclerosis.

In June 1971 six Lipid Research Clinics were funded after review from the 32 proposals received in response to RFP-NHLI-71-3 (Lipid Research Clinics). These six clinics have now all been operational for one year.

During this time, they have achieved several program goals that include:

1. The creation of a functional inter-clinic organizational structure with the Program guided by an executive committee (consisting of the Lipid Research Clinic Directors and chaired by the Program Office) and supported by seven active standing committees (consisting of at least one representative from each Lipid Research Clinic) Laboratory Methods, Cardiovascular Endpoints, Intervention, Pediatrics-Genetics, Collaborative Studies, Definitions and Forms Design, and Nutrition.

2. The development of a two-volume Reference Manual for the Lipid Research Clinic which carries instructions for all laboratory methods, definitions of hyperlipoproteinemia in its various forms, detailed basic prevalence designs, instructions for all inter-clinic data collection and reporting forms and all common study protocols.

3. The design and approval by the executive committee of a clinical trial to test the "lipid hypothesis of atherosclerosis." The intervention protocol as now written, will be a primary prevention trial. It will be done in all clinics on open populations of Type II subjects. Endpoints will be those of death presumed due to coronary heart disease or of non-fatal myocardial infarction. It will be based on the use of specific lipid-lowering drugs and will be double blind. As currently planned, the trial will involve 3,600 male subjects, 35-59 years old (300/clinic) and will last for 5-7 years. Exclusions will include evidence of CHD, hypertension, and diabetes. Stratification will probably be done by smoking history, age, cholesterol level, and exercise EKG. The subjects will then be randomized into drug or placebo groups.

4. The selection after review including site visits by the Lipid Research Clinic Directorate of a single laboratory for all secondary tests by all Lipid Research Clinics during the prevalence studies.

5. The evaluation of basic systems for the determination of cholesterol and triglyceride and the modification of one of these systems so that it now holds promise as a high-volume reference method.

6. The creation of a detailed system for quality control and standardization that involves three different phases, and which will be admirably suited to self-evaluation as well as to monitoring by the Central Patient Registry.

7. The design of compatible prevalence studies at all six Lipid Research Clinics that in planning and design will lead to easy pooling and central data collection.

8. The standardization of one submaximal exercise stress test for all Lipid Research Clinics. This and identical questionnaires to be used in all clinics will insure uniformity of evaluation for vascular disease.

9. The finalization and approval by the Lipid Research Clinics, Program Office, and Office of Management and Budget of a series of forms to be used for all Lipid Research Clinic patients in all studies.

This year RFP-NHLI-72-1 "Lipid Research Clinics" was distributed widely on September 20, 1971. Thirty-nine letters of intent were received and 30 proposals were reviewed for their scientific excellence and relevance to the Program goals by an ad hoc technical panel of 12 research scientists representing the fields of lipid metabolism, clinical pharmacology, nutrition, cardiology, pediatrics, epidemiology, clinical chemistry, and biostatistics. Thirteen of the initial 30 proposals were site visited and extensively reviewed. After three full meetings of the technical review panel, six proposals were recommended for funding and evaluation. The Program Office concurred with the panel recommendations which were sent to the Directorate of the National Heart and Lung Institute. These six proposals recommended for funding are now undergoing scientific discussion and formal contract negotiations. It is hoped that these six additional clinics will complete all contract negotiations and be funded by June 15, 1972.

The six additional Lipid Research Clinics will complete the network of regional Lipid Research Clinics. They will provide the additional patients needed for the proposed intervention trial (an estimated 3,600-4,000 patients) and amplify the clinics sampling frame for prevalence studies.

The Lipid Research Clinics program is projected to continue for 5-8 years. The objectives for this coming year include: 1) establishment and maintenance of core laboratories capable of accurate quantitative measurements of plasma lipids and lipoproteins, 2) standardization of all Lipid Research Clinics in terms of basic techniques and terminology, 3) commencement of prevalence studies designed to define the prevalence of the different types of familial and sporadic hyperlipoproteinemia and their coexistence with coronary vascular disease, 4) development in all clinics of standardized cardiac exercise laboratories capable of performing and analyzing up to thirty exercise tolerance tests weekly, 5) completion of the planning and design for a common multicentric intervention trial designed to test the lipid hypothesis, 6) establishment of clinical facilities in which both children and adults with hyperlipoproteinemia can be

detected, evaluated, and treated while the family is followed as a unit, 7) development of data management capabilities at all clinics for integrating patient records and communicating with the Central Patient Registry on an ongoing basis, 8) development and evaluation of methods for dietary counseling, evaluation, and monitoring, 9) establishment of each Lipid Research Clinic as a regional resource and reference laboratory for lipid and lipoprotein methodology and as a dietary and clinical consultation service for patients, physicians, dieticians, and nurses, 10) evaluation of current techniques for the diagnosis of hyperlipoproteinemia and the development of better ones, 11) development of as many common protocols and collaborative ties among the Lipid Research Clinics as possible.

Since the Lipid Research Clinics have not had the opportunity in the brief time since their funding to establish an identity separate from that of the collaborative program, it is considered premature to describe their accomplishments separately in this 01 Year. Their objectives, major findings, significance and proposed course are described above.

University of Alabama
Birmingham, Alabama
Contract No. NIH-71-2159
Principal Investigator: Robert Kreisberg, M.D.
Contract Amount: $390,435 (6/24/71 - 6/22/72)
Projected Funding: 5-8 Years (With Annual Review and Renewal)

Baylor College of Medicine
Houston, Texas
Contract No. NIH-71-2156
Principal Investigator: Antonio Gotto, Jr., M.D.
Contract Amount: $400,000 (6/29/71 - 6/28/72)
Projected Funding: 5-8 Years (With Annual Review and Renewal)

University of California, San Diego
La Jolla, California
Contract No. NIH-71-2160
Principal Investigator: Daniel Steinberg, M.D.
Contract Amount: $410,000 (6/29/71 - 6/28/72)
Projected Funding: 5-8 Years (With Annual Review and Renewal)

Johns Hopkins University
Baltimore, Maryland
Contract No. NIH-71-2158
Principal Investigator: Peter Kwiterovich, M.D.
Contract Amount: $350,465 (6/14/71 - 6/13/72)
Projected Funding: 5-8 Years (With Annual Review and Renewal)

Leland Stanford Junior University
Palo Alto, California
Contract No. NIH-71-2161
Principal Investigator: John Farquhar, M.D.
Contract Amount: $409,873 (6/22/71 - 6/21/72)
Projected Funding: 5-8 Years (With Annual Review and Renewal)

University of Washington
Seattle, Washington
Contract No. NIH-71-2157
Principal Investigator: Edwin Bierman, M.D.
Contract Amount: $379,290 (6/24/71 - 6/23/72)
Projected Funding: 5-8 Years (With Annual Review and Renewal)

THE CENTRAL PATIENT REGISTRY AND COORDINATING CENTER

The Central Patient Registry and Coordinating Center was funded at the University of North Carolina, Chapel Hill, North Carolina, in late June 1971 (in response to RFP-NHLI-71-17) to help plan and design all reporting forms, collect edit, monitor, and store all data, and help coordinate the collaborative program of the Lipid Research Clinics.

The objectives of the Central Patient Registry include:

1. The acquisition, analysis, and storage of data on hyperlipoproteinemia prevalence especially among young age groups with special emphasis on the nature and frequency of genetic forms.

2. Acquisition, analysis and storage of data on the prevalence and incidence of atherosclerosis in the different types of hyperlipoproteinemia.

3. Study of the natural history of subjects with hyperlipoproteinemia, especially the familial types.

It has the responsibility of establishing a Patient Registry and Coordinating Center for the Lipid Research Clinics which will serve as: 1) Central Patient Registry for all patients with hyperlipoproteinemia discovered by the Lipid Research Clinics, 2) Coordinating Center for collaborative clinical trials of hypolipidemic agents, 3) Central Laboratory monitor.

The Central Patient Registry has been extremely active during this initial year of funding. It has collaborated with the Lipid Research Clinics in the writing of the two-volume Manual of Operations for the Lipid Clinic Program and has taken on much of the responsibility for editing, collating, and printing the manual. It has played a central role in the writing, preparation, compilation, and design of the forms to be used in the prevalence protocols. These forms have all been approved by the Lipid Clinic Directorate and the Office of Management and Budget and are now being printed by the Central Patient Registry.

The Central Patient Registry has also been actively involved in the design of all the prevalence studies. It has participated in the establishment of the quality control criteria and is responsible for the data analysis of the recent cholesterol-triglyceride trials and the quality control surveillance program of the Lipid Research Clinics.

Over the next year, the workload of the Central Patient Registry will expand considerably with the entry of additional Lipid Research Clinics into the program. Increased demands will occur in the fields of reception, storage, analysis and editing of data as the prevalence studies get underway with their standardized forms, laboratory analyses and submaximal exercise testing. The Registry will have an increased number of clinics to integrate and periodically visit.

The Central Patient Registry will be especially concerned over this next year with the Lipid Research Clinic intervention trial. It will be responsible for devising the specifications of the study, for the design and maintenance of the forms and data base, for developing and maintaining randomization procedures, safety monitoring, etc.

The operational objectives of the Central Patient Registry this coming year include: 1) maintanence and supervision of an internal and external quality control surveillance program for the Lipid Research Clinics, 2) standardization of new Lipid Research Clinics according to established procedures of data collection and preparation, 3) assistance and guidance for new Lipid Research Clinics in the development of prevalence studies and for existing clinics in data analysis for ongoing prevalence studies, 4) development of more detailed plans for intervention studies, including the development of study specifications and standardization of procedures, randomization techniques, monitoring for patient safety, data quality and compliance, 5) provision of progress reports for the Lipid Research Clinics and the Program Office summarizing the amount of screening and the quality of the work submitted, 6) assistance in the evaluation of quality control for exercise stress testing and laboratory determinations of "secondary tests," 7) development and evaluation of statistical methods and data management techniques useful in the handling of various data for linkage problems, 8) maintenance of an operational Central Patient Registry to collect data on disease prevalence, disease incidence, and patient characteristics in specific types of hyperlipoproteinemia.

University of North Carolina
Chapel Hill, North Carolina
Contract No. NIH-71-2243
Principal Investigator: James E. Grizzle, Ph.D.
Contract Amount: $206,000 (6/28/71 - 6/27/72)
Projected Funding: 5-8 Years (With Annual Review and Renewal)

ANNUAL REPORT

RESPIRATORY DISEASES BRANCH

July 1, 1971 through June 30, 1972

Introduction

The Respiratory Diseases Branch was established January 1971. This Branch fosters collaborative research and development programs which complement current research supported from other sources. The Branch emphasizes aspects of respiratory disease problems that are timely, have promise of leading to results of practical significance.

Studies may be either fundamental or clinical, and targeted to practical problems such as developing methods for the earliest detection of disease.

Objectives of the Branch

The Branch fosters collaborative research either fundamental or clinical targeted to practical problems such as (1) developing methods for the earliest detection of the disease or diseases prior to the occurrence of irreversible disease; (2) the relation of smoking to pulmonary disease, (a) using animal models or (b) human studies; (3) to stimulate population studies to determine prevalence of chronic pulmonary disease in arbitrarily selected populations, which can be hospital, organization, occupational or geographically based in the United States or elsewhere. These studies will identify populations for epidemiologic studies other than prevalence studies (4) to study host factors as determinants of chronic obstructive pulmonary disease (COPD) susceptibility (a) in hospital populations, (b) in community based populations, and (c) in pedigrees; (5) to stimulate studies for the improvement of treatment, care, and rehabilitation of patients with advanced chronic respiratory diseases.

During the first year of the Respiratory Diseases Branch two requests for proposals were circulated. One was on Oxygen Therapy vs. Oxygen Toxicity and Methods of Ventilating Assistance. This was issued February 9, 1971. This group of contracts are included in the Treatment Area of the Branch Program. The second request was for Alpha$_1$ Antitrypsin Deficiency and Chronic Respiratory Disease. These contracts are included under the Pathogenesis Subprogram in the Respiratory Diseases Branch.

The Treatment Program

The O_2 Toxicity vs. Therapy contracts placed emphasis on: (1) the effect of O_2 on metabolic pathways and surfactant synthesis; (2) determination of maximum time limit of exposure; (3) cellular response to O_2 exposure; and (4) the effect of O_2 exposure on mucociliary function.

Significance

To understand the mechanism of O_2 toxicity and its effect on metabolic pathways and surfactant synthesis is essential to the problem of pulmonary edema.

Pathogenesis Program

Objectives:

This part of the program is related to understanding the history of the diseases; the development of early diagnostic tests; the study of prevalence of the disease; the relationship of smoking to COPD; occupational exposures and to the study of host factors as determinants of COPD in various selected populations.

The alpha$_1$ antitrypsin contracts are included in this part of the sub-program. Alpha$_1$ antitrypsin is a genetic deficiency, therefore, one of a number of other unknown host factors, which when identified will assist in biologically characterizing that portion of the population at risk to this group of diseases.

The objectives of this group of contracts are to determine (1) the prevalence of the association of the deficiency in a population and (2) the role of heterozygosity in the pathogenesis of chronic respiratory disease, (3) the genetic frequencies of the various phenotypes, and (4) the associations of chronic respiratory disease in persons with odd phenotypes.

Treatment - Oxygen Contracts

Proposals for work on O_2 Therapy vs. O_2 Toxicity have been supported during 1971-72. The program has the following features: some of the contracts focus on cellular constituents and biochemical pathways affected by high O_2 exposure. Other contracts concentrate on the mechanics of O_2 toxicity and include correlation of biochemical and pathological observations. Still other contracts are focused on the lipid metabolic pathways and surfactant synthesis which are of importance to problems related to O_2 toxicity. Another contract evaluates the possibility of the synergistic effect of respiratory infection and O_2 exposure in producing a toxic response. Another will attempt to determine maximum limits of exposure for specific oxygen pressure and safe levels of exposure. Finally, one contractor is studying the effect of O_2 exposure on mucociliary function and the mode of oxygen administration.

Title of Contract:	To Conduct Studies on the Effect of Oxygen Toxicity and Methods of Ventilatory Assist
Number of Contract:	NIH 71-2205
Organization:	Mt. Sinai Hospital Miami Beach, Florida
Project Director:	Marvin A. Sackner, M.D.
FY'71 Support	$33,540 June 15, 1971 - June 14, 1972
Proposed Course:	Renewal recommended 1972 - 1973

The objectives of this contract are (1) to study the effect of oxygen and humidity on mucous clearance rates in the dog by the use of a bronchofiberscope, and (2) to ascertain the effect of graded inspired O_2 clearance in patients who have endotracheal tubes, having had, open heart surgery.

Results to date

The results indicate that the mucous flow rate is inhibited by graded inspired O_2, and that phrenic stimulation given to non-intubated dogs via electrodes in the neck vein produced adequate breathing for several hours.

Significance

Respiration may be maintained adequately during open heart surgery in man by using the phrenic nerve stimulators for continued respiration eventually.

Title of Contract:	Study Effects of Oxygen Toxicity on Lung Cell Division
Number of Contract:	NIH 71-2151
Organization:	Rancho Los Amigos Hospital Downey, California
Project Director:	Jack D. Hackney, M.D.
FY'71 Support:	$20,905 June 15, 1971 - June 14, 1972
Proposed Course:	Recommended for renewal 1972 - 1973

Objectives

This contract fulfills the objectives of this part of the program. They are studying the effects in primates of allowed concentration on turnover times of alveolar cells, and determine a dose response relationship for various concentrations of 12-100% of oxygen in nitrogen.

The ultimate goal of this contract is to provide guidelines for the safe use of oxygen by understanding the mechanisms of oxygen-produced lung damage.

Results to date

Twenty-three animals who had been exposed to 60% oxygen, and 22 who had been exposed to 80% oxygen were sacrificed for none died during the experiment. No evidence of edema or hyaline membranes was observed in the lungs of the exposed or control animals when exposed to concentrations of 40, 60, or 80% oxygen in nitrogen.

Title of Contract:	Mechanisms of Structural-Functional Defects in Pulmonary Oxygen Toxicity
Number of Contract:	NIH 71-2152
Organization:	Albert Einstein College of Medicine of Yeshiva Univ. Bronx, New York
Project Director:	Robert M. Rosenbaum, Ph.D.
FY '71 Support:	$120,630
Proposed Course:	Recommended for renewal FY '72-'73

The goals of this contract are to study the effects of O_2 toxicity and induced tolerance to O_2 on pulmonary surfaction on rats and hamsters, to study pulmonary surfactant synthesis in acute pulmonary O_2 toxicity during adaptation to O_2 and during air recovery from O_2 exposure following adaptability to study chemistry of function; to study chemistry of pulmonary homogenetics; to study the effects of O_2 ribsomal--RMA processing in a cell culture model system; and to study the effects of toxic O_2 levels on protein synthesis in a model cell system.

Results to date

Major results thus far are (1) indication of tolerance to O_2 permiting survival of the animal in otherwise lethal concentrations of O_2, either by a marked increase in phospholipid synthesis or by a decrease in its elimination; (2) increased phosopholipid synthesis in O_2 tolerant animals could stabilize the alveoli against edema formation and/or development of atelectasis; and (3) exposure to toxic O_2 concentrations produces relatively little loss in surface tension, while simple induction of tolerance to O_2 alone has little effect on surface tension.

Title of Contract:	Study Effect of O_2 on Lung Surfactant Production
Number of Contract:	NIH 71-2153
Organization:	Memorial Hospital Pawtucket, Rhode Island
Project Director:	Dr. Ralph A. Redding
FY '71 Support:	$52,026 - June 15, 1971 - June 14, 1972
Proposed Course:	Renewal recommended

This contract is targeted to study mechanisms by which oxygen causes lung damage, to identify methods of detection prior to the occurrence of irreversible oxygen toxicity; physiologic, biochemical, and pathological methods will be used to study the effects of varying concentrations of oxygen upon lung production lung surfactant.

Results to date

They have found that rats exposed to 70% oxygen for 10 days have pulmonary edema determined by the depressed dry/wet lung ratios; increased macrophages are observed, and biochemical changes in some parameters noted. In spite of the above changes, no significant changes were noted in lung compliance or hysteresis.

Title of Contract:	To Determine the Biochemical and Pathological Changes in the Lungs of Animals Subjected to Prolonged Exposure to Oxygen Pressure
Number of Contract:	NIH 71-2154
Organization:	Duke University Durham, North Carolina
Project Director:	Aaron P. Sanders, Ph.D.
FY '71 Support:	$49,829, June 15, 1971 - June 14, 1972
Proposed Course:	Renewal recommended 1972 - 1973

The main objectives of this program are to study the biochemical functions of respiration, oxidative phosphorylation, certain Krebs cycle enzyme systems, ATP concentration, ATP ase activity, and surfactant properties. Efforts will be made to determine if there is a cardiopulmonary interrelationship in pulmonary oxygen toxicity.

Results to date

1. A marked decrease in ATP concentration noted on the lung in rats exposed to 1.5 ATA O_2 or ATA O_2.

2. A decrease in lung ATP concentration precedes the marked effects of CNS O_2 toxicity which occurs between 10 and 20 hours at 2 ATA O_2, 24-30 hours at 1.5 ATA O_2.

From these observations it would appear that the primary event in pulmonary O_2 toxicity is the interference with ATP production resulting in decreased ATP insufficient to sustain normal cell function.

Significance to Biomedical Research

Further study on this problem may well give us the answer to some of the parameters that affect O_2 toxicity and its effect on the lung. This would be a most important step in understanding the problem of O_2 toxicity.

Title of Contract:	To Conduct Studies on Respiratory Infections and O_2 Toxicity
Number of Contract:	NIH 71-2155
Organization:	IIT Research Institute Chicago, Illinois
Project Director:	Dr. Richard Ehrlich
FY '71 Support:	$53,250, June 15, 1971 - June 14, 1972
Proposed Course:	Renewal recommended for 1972-1973

This contract is targeted to conduct studies to determine the interactions of respiratory infections and oxygen toxicity.

Swiss Webster mice will be exposed to varying concentrations of oxygen. The infections challenges will be made at various time periods before, and after the oxygen exposure. The oxygen concentrations are 100, 50, and 60 percent ATA.

The titers of pneumonia virus of mice PVM, K virus, reovirus type 3, polyoma, H-1, Kilham rat virus, mouse hepatitis, mouse adenovirus, and lymphocytic choriomeningitis were less than 1:10. Assays for these antibodies were not performed in the replicate experiment except for PVM, since this virus propagates in the lung.

Pathogenesis - Alpha$_1$ Antitrypsin

Alpha$_1$ antitrypsin forms an important part of the branch program. The contracts supporting work on alpha$_1$ antitrypsin deficiency and the relationship of the deficiency to respiratory disease, constitutes a program within the Branch and comes under the subprogram heading of pathogenesis.

Contracts for the establishment of two reference laboratories were funded. The function of these laboratories, as they develop their capabilities, would be to standardize, to the greatest extent possible, techniques being employed to quantitate the alpha$_1$ antitrypsin serum phenotypes. This would be done by the use of starch gel electrophoresis, crossed antigen body electrophoresis, as well as by immuno-fixation electrophoresis.

They will be able to do a large number of analyses and will also carry on research on new techniques and on identification of new phenotypes. Other contracts related to alpha$_1$ antitrypsin are involved in general population studies. At two institutions populations are divided into several categories. They will be studied in depth for detecting respiratory disease at an early stage and for phenotype identification.

In arizona, an area with a high prevalence of COPD, a patient population with chronic respiratory diseases are being studied for the genetic aspects of the disease. Another institution is studying a population consisting of children and young adults and a third institution is concerned with the prevalence of COPD and genetic variants in a black population.

Title of Contract:	Family Study of Alpha$_1$ Antitrypsin
Number of Contract:	NIH 71-2216
Organization:	Johns Hopkins University Baltimore, Maryland
Project Director:	Bernice H. Cohen, Ph.D.
FY '71 Support:	$30,000, June 15, 1971 - June 14, 1972
Proposed Course:	Recommended for renewal, 1972-1973

Objectives

The project will carry out an intensive study of kindreds of individuals with depressed levels of alpha$_1$ antitrypsin and/or structural variants of alpha$_1$ antitrypsin (Pi phenotypes) and a suitable comparison series in order to explore the familial occurrence of alpha$_1$ antitrypsin, COPD, and their interrelationship.

Results to date

The collection of data and bloods on COPD index subjects and comparison subjects is in accordance with the parent study design. The investigation has been expanded to include families referred from outside sources into the alpha$_1$ antitrypsin family study because of known or suspected alpha$_1$ antitrypsin variants. These subjects are being incorporated into the investigation. Screening of a series of 800 bloods from a general population in Washington County, Maryland for the alpha$_1$ antitrypsin defect has been initiated. Three more genetic factors will be studied in the index cases.

Significance

This kind of study is an important step in the identification of those persons in a population who are at risk to developing COPD.

Title of Contract:	Reference Laboratory for the Study of Alpha$_1$ Antitrypsin
Number of Contract:	NIH 71-2217
Organization:	Massachusetts General Hospital Boston, Massachusetts
Project Director:	Richard C. Talamo, M.D.
FY '71 Support:	$36,670, June 15, 1971 - Junr 14, 1972
Proposed Course:	Recommended for renewal, 1972-1973

Objectives

This contract will develop one of two resource laboratories for the study of alpha$_1$ antitrypsin and its electrophoretic variants. This laboratory will be able to quantitate the alpha$_1$ antitrypsin serum phenotypes using the starch-gel electrophoresis, and crossed antigen-antibody electrophoresis and by immuno-diffusion electrophoresis.

This laboratory will also attempt to standardize all procedures, and help other laboratories to do so. Therefore, it will be possible for all laboratories working on this problem to compare their results.

Results to date

Representatives from other laboratories have spent time in this reference laboratory, as in the other one, learning techniques. In addition, three non-contract investigators have received similar instruction. This laboratory has developed techniques for the functional assay of antitryptic activity. They have, thus far, identified MM, MZ, ZZ, MS, IM, SZ, FF, FM, MV, and MX types.

Title of Contract:	Studies of Proteinase Inhibitor Phenotypes
Number of Contract:	NIH 71-2218
Organization:	Washington University School of Medicine St. Louis, Missouri
Project Director:	John A. Pierce, M.D.
FY '71 Support:	$69,201, June 15, 1971 - June 14, 1972
Proposed Course:	Recommended for renewal

Objectives

The objectives of this contract were to establish a second reference laboratory for the purpose of standardizing procedures to be used by other contract laboratories as a reference, and to give training to the staff of these contractors' laboratories and other laboratories seeking this training.

The laboratory would also determine gene frequencies of proteinase inhibitors (antitrypsin) alleis in several population groups; index and examine subjects and families of subjects with odd proteinase inhibitor phenotypes in an effort to determine a relationship to COPD or other pulmonary diseases; would utilize the starch-gel method of antitrypsin analysis for the acquisition of knowledge about the inhibitor.

Results to date

The laboratory has been established. Other contractors have received training in phenotyping techniques, and representation from four non-contract laboratories have also received assistance.

One hundred and 71 sera samples from other institutions have been analyzed. In addition, a batch of standard "unknown" reference samples have been circulated to other contract labs to insure comparability.

Since December 1971, 900 blood donor sera from the Barnes Hospital Blood Bank have been studied using the starch-gel electrophoresis method, all done in duplicate. Seventy-five samples of these 900 have been examined by crossed immuno electrophoresis. Out of these 75 samples they have identified 36 individuals with "S" (slow) alleles, and nine individuals with "Z" alleles. The total sample required for a definitive population survey in St. Louis will probably be in the neighborhood of 2,000 samples.

From the present data, it appears that gene frequency for S is about the same as reported from Scandinavia, while the gene frequency for Z is somewhat lower. These are preliminary results.

Extensive family studies have revealed three families with unusual phenotypes. The correlation of COPD with various allelic patterns is being pursued.

Title of Contract:	Study of Genetic Predisposition to Chronic Obstructive Lung Disease
Number of Contract:	NIH 71-2219
Organization:	University of Arizona Tucson, Arizona
Project Director:	Benjamin Burrows, M.D.
FY '71 Support:	$49,100, June 15, 1971-June 14, 1972
Proposed Course:	Recommended for renewal, 1972-1973

Objectives

The objective of this contract is to determine the importance of genetic factors in predisposing to COPD and the importance of alpha$_1$ antitrypsin

deficiency in this genetic predisposition.

Results to date

No hard data presented this year. Procedures for alpha$_1$ antitrypsin testing (TIC and P$_1$ testing) were developed; epidemiologic methods for the project were designed and a pilot project of 101 subjects was completed. The questionnaires and procedures were changed on the basis of the pilot study findings. Data collection on population will now be started.

Title of Contract:	Study of Alpha$_1$ Antitrypsin and Respiratory Disease
Number of Contract:	NIH 71-2220
Organization:	University of Oklahoma Foundation Oklahoma City, Oklahoma
Project Director:	James F. Hammarsten, M.D.
FY '71 Support	$50,965, June 15, 1971-June 14, 1972
Proposed Course:	Recommended for renewal, 1972-1973

Objectives

The objectives are to assess overlap of trypsin inhibition capacity (TIC) determination in separating heterozygotes from normals; to determine the prevalence of heterozygotes and homozygotes in the identified population, to determine the distribution of various phenotypes; to assess the prevalence of respiratory disease in a group of homozygote deficient subjects, and a group of heterozygote subjects and a group of normals; to compare the distribution of various phenotypes in Caucasians, Indians, and Blacks.

Results to date

Screening began in Seminole County in September 1971 and in Muskogee County in January 1972. Blood samples numbering 2,600 have been drawn and 1,552 analyzed for alpha$_1$ antitrypsin deficiency. The response rate is around 60% of those bloods with TIC determinations; 209 are in the intermediate range; and three are homozygous deficient (less than 0.4). The investigators project 500 subjects in the intermediate range by the end of the study.

Exchange of samples with the Washington University reference laboratory has been instituted. Phenotyping determinations are planned for all abnormal subjects.

The survey which will be conducted by means of respiratory questionnaire and pulmonary function testing will begin in April 1972.

Significance

No inferences can be made from the results so far. The sample is too small to date. The questionnaire survey and pulmonary function testing correlated with the TIC determinations should give us some hard data in the coming year.

Title of Contract:	Study of Alpha$_1$ Antitrypsin and Chronic Respiratory Disease
Number of Contract:	NIH 71-2221
Organization:	University of Rochester Rochester, New York
Project Director:	Robert H. Schwartz, M.D.
FY '71 Support:	$100,000, June 15, 1971-June 14, 1972
Proposed Course:	Recommended for renewal, 1972-1973

Objectives

The objectives of the contract are to study the relationship between alpha$_1$ antitrypsin and chronic respiratory disease. The population will be selected from the roster of the Rochester Child Health Survey (RCHS) and the Early Disease Detection Units (EDDU). Approximately 200 persons will be studied. The hypothesis that heterozygous subjects for alpha$_1$ antitrypsin deficiency are more likely to have lung disease than subjects with normal alpha$_1$ antitrypsin levels will be tested. They will try to establish the prevalence of heterozygous alpha$_1$ antitrypsin deficiency and the various Pi genotypes in patients with emphysema. They are also concerned with the development of original approaches to the diagnosis of heterozygous alpha$_1$ antitrypsin deficiency.

Serological studies will include quantitative alpha$_1$ antitrypsin levels using an immunological and a biochemical assay, with genetic typing by acid starch electrophoresis and crossed antigen-antibody electrophoresis.

Results to date

In the Rochester Child Health Survey population 52 subjects have been studied with questionnaire, pulmonary function testing, TIC determinations and phenotyping, and four intermediate level subjects have been identified.

The population from the EDDU and emphysema patients numbered 521. Similar protocol was used as for the Rochester Child Health Survey. In this group 23 heterozygotes and one homozygote deficient subject were found.

In addition, several families have been studied in detail, but no figures are available at this time.

Significance

Insufficient data at this time does not allow for an analysis of the data on hand.

Title of Contract:	Study of Prevalence of Alpha$_1$ Antitrypsin Deficiency in a Black Population
Number of Contract:	NIH 71-2222
Organization:	Howard University Washington, D.C.
Project Director:	Robert Hackney, M.D.

FY '71 Support: $41,000, June 15, 1971-June 14, 1972
Proposed Course: Recommended for renewal, 1972-1973

Objectives

The objectives of this contract are: (1) to determine what is the normal range of alpha$_1$ antitrypsin in a black population; and (2) to determine what is the incidence of antitrypsin deficiency in the same population.

To accomplish their objectives they will make serum alpha$_1$ antitrypsin determinations in 200 normal black children and adults, and in 200 patients with COPD. Normalcy will be established by pulmonary function studies including: VC, Timed Vital Capacity at both one and three seconds, Forced Expiratory Flows at 200-1200 mls., and Maximum Voluntary Ventilation.

They will use the standard techniques for the serum alpha$_1$ antitrypsin levels; assay for trypsin inhibitory capacity and electrophoresis on cellulose acetate followed by densitometry. A third method of quantification by radioimmunoassay will be developed and evaluated. All subjects will be studied by each of the three methods.

Results to date

The total subjects studied so far number 126. The investigators have had difficulty in obtaining normal subjects.

They have noted that there appears to be an absence of intermediate deficient or homozygous deficient subjects. They have also noted unusually high values in the subjects studied compared to the published TIC values.

They have not yet completed an inter-laboratory exchange with the University of Washington laboratory, nor have they received results from the samples which they have sent. This must be accomplished before they can validate the higher TIC values in this particular population.

New Programs

The Chronic Disease Branch is targeted to engage in studies on prevalence, cause, treatment, and prevention of chronic respiratory diseases, on a national scale.

New RFP's were written since January 1972 to further the above mission. The Branch's program is divided into several subprograms. These are pathogenesis, disease mechanisms, and treatment.

The first RFP, NHLI 72-24, issued on February 14, 1972, was related to smoking and chronic airways obstruction. It was directed to the evaluation of a new diagnostic technique. Closing volume, which offers an opportunity, if validated to make early diagnosis of COPD a reality, and intervention at

that point in time might reverse the disease process itself.

Another RFP, NHLI 72-25, was issued February 14, 1972, and is also part of the subprogram of pathogenesis. The title was "Chronic Pulmonary Disease and Smoking (Animal Models)." There is need to develop suitable animal models for the express purpose of studying the slow progressive effects and structural changes that smoking produces on the lungs under varying conditions. This is more readily accomplished in animals as is the ability to obtain quick structural confirmation of the changes.

A third RFP, NHLI 72-27 was issued on February 14, 1972. This was titled "Population Studies on Respiratory Diseases." This RFP is also part of the pathogenesis program, subprogram-epidemiology. The objective of this particular RFP was to stimulate interest in the effect of smoking combined with various external factors on the prevalence of COPD in defined populations such as entire communities, hospitals, or occupational groups. These populations, once identified, can be further studied for host determinants. On March 1, 1972, a fourth RFP was issued. This RFP, NHLI 72-28, is a case control study on host factors as determinants of COPD susceptibility. It is also in the subprogram of pathogenesis. A need for the study of factors, intrinsic to the host, has not received sufficient attention. The biologic markers that differentiate individuals from each other and from groups within a population have had little emphasis. These markers include genetic, immunologic, and endocrine patterns which when determined, may assist in defining that portion of the population at risk with respect to CRD within the total population.

Collaboration with the NCI

The Respiratory Diseases Branch will collaborate with the Cancer Institute on an animal smoking study. The beagle dog is the experimental animal to be used. These dogs will be conditioned to smoke via a tracheotomy.

The purpose of this proposal is to determine whether nicotine is importantly involved in the harmful effects on the lungs of beagle dogs who are given daily inhalation of special cigarettes, with determined nicotine contents over many months.

The types of cigarettes to be tested will be produced by the NCI. Two types are to be provided. One type, hereafter designated as HN, will contain a very high amount of nicotine. The two types (HN and LN) will deliver approximately the same amount of tar (exclusive of nicotine). The amount of tar should be in the range of 30 mg. per cigarette which is 5 mg. less than the amount delivered by the non-filter tip cigarette used in the previous experiment.

The tar from both types should be active in the production of cancer when applied to the skin of rodents.

Smoke from type HN should contain 1.85 mg. of nicotine per cigarette. This is the amount delivered by the non-filter cigarettes used previously.

Smoke from type LN should contain very little nicotine (0.2 mg. or less). Both types of cigarettes should be made of flue cured tobacco (or mainly flue cured tobacco), and the smoke should be neutral or very slightly on the acid side.

The support will be for a maximum of two years at $700,000 per year.

ANNUAL REPORT
OF
SICKLE CELL DISEASE BRANCH

July 1, 1971 through June 30, 1972

BRANCH SUMMARY

Background

In March, 1971, the Sickle Cell Disease Branch was established subsequent to the President's Health Message to the Nation in February, 1971, in which sickle cell disease was targeted as a major health problem. Special appropriations were made to bring about a coordinated effort within the Department of Health, Education and Welfare to effect a multi-categorical attack on this disease from the standpoint of research and service. The major agencies involved in this coordinated effort would be the NIH and HSMHA but not limited to HEW alone. The Department of Defense and the Veterans Administration also would be intimately involved. At the direction of the Secretary, DHEW the NIH was named the lead agency in this coordinated effort and the NHLI was named the lead Institute within the NIH.

Following the establishment of the Sickle Cell Disease Program, the Sickle Cell Disease Advisory Committee was named with the purpose of recommending guidelines for the sickle cell disease effort. It was recommended and accepted that the funds earmarked for this program be divided equally between research and service and that these areas would include basic and clinical research, diagnosis, clinical application and trials, and community services consisting of screening, education, counseling and training. In addition an information center would also be developed as a component of the program.

The Sickle Cell Disease Branch will as such plan, develop and direct a collaborative program of research to expand and improve diagnosis, therapy and prevention of sickle cell disease, both at the fundamental and clinical levels and to initiate and expand community education and screening programs through demonstration clinics located at strategic places across the country.

BASIC AND CLINICAL RESEARCH, CLINICAL TRIALS OF THERAPY

These goals of the Sickle Cell Disease Program were initiated in FY 71 with the issuance of an RFP by the Blood Resources Branch to investigate clinical trials of therapy for sickle cell vaso-occlusive crises (NHLI-71-8). This was followed by Basic and Clinical Research (studies in sickle cell disease RFP NHLI-72-5). Both of these studies are outlined in the annual report of the Blood Resources Branch.

SCREENING AND EDUCATION CLINICS

The purpose of this program is to obtain information to ascertain the most efficient means of carrying out screening and educational procedures under various conditions and circumstances. To obtain a broader concept of how to

do this twenty Screening and Education Clinics will be set up across the country with the objectives of increasing public awareness regarding this disease; to detect persons with sickle hemoglobin and to further definitively classify them (trait, variant, anemia, etc.); education of involved persons, affected and non-affected; offer counseling information as necessary; to assist in obtaining proper follow-up for affected persons; and to analyze the results of these approaches. Information derived from these demonstration or model clinics will then be utilized as guidelines for establishing future programs.

This program will be administered through the HSMHA agency. In January, 1972, announcements of this program were sent out and 77 applications were received. These applications are currently undergoing review and final announcements of awards will be made around June 1, 1972 followed subsequently by contract negotiations.

RESOURCE DEVELOPMENT

Sickle Cell Disease Information Center

Plans for implementing a Sickle Cell Disease Information Center are being designed to accumulate and subsequently classify and disseminate information on this problem. It is anticipated that action on this program will begin in June, 1972.

Sickle Cell Disease Manpower Resource Development

Effective programs in education and counseling in sickle cell disease will depend upon the utilization of persons knowledgeable in these aspects. The purpose of this program is to provide expertise to professionals and allied health professions that they may then train others to carry out these program aspects. Plans for implementing this component of the program are being developed and it is anticipated that this program will be started in July 1972.

CLINICAL APPLICATIONS PROGRAM

July 1, 1971 through June 30, 1972

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REPORT OF ASSOCIATE DIRECTOR FOR CLINICAL APPLICATIONS, NHLI
July 1, 1971 - June 30, 1972

The Clinical Applications Program is comprised of the Office of the Associate Director and three branches: Biometrics Research Branch, Epidemiology Branch and the Therapeutic Evaluations Branch.

Office of the Associate Director for Clinical Applications: Dr. W.J. Zukel
Biometrics Research Branch: Chief, Dr. Max Halperin
Therapeutic Evaluations Branch: Acting Chief, Dr. W.J. Zukel
Epidemiology Branch: Chief, Dr. Manning Feinleib
Framingham Heart Disease Epidemiology Section: Chief, Dr. W.B. Kannel
Field Epidemiology Research Section: Chief, Dr. Manning Feinleib
Geographical Diseases Section: Chief, Dr. W.J. Zukel

During the year, the professional and supporting staff of 60 members have continued to participate in direct research and collaborative research with emphasis on epidemiological studies, biostatistical research and clinical trials relating to cardiovascular diseases and lung diseases. The relative allocation of research effort by disease categories is indicated below:

Disease Areas	Percent of Program Activities
Atherosclerotic Coronary Artery Disease including Angina Pectoris, Myocardial Infarction, Sudden Unexpected Death, and Pathological Studies of Atherosclerosis	50
Hypertension & Hypertensive Vascular Disease	20
Cerebrovascular Disease	10
Chronic Obstructive Respiratory Disease	10
Peripheral Vascular Disease, Diabetes, Other	10

The direct research and collaborative research activities within the Clinical Applications Program make use of several research support mechanisms including direct funds, contract funds, research grants and P.L. 480 counterpart currency funds. Staff participation with NHLI investigators and with outside scientists is considerably increased by access to this variety of mechanisms.

Highlights of research activities during the year are summarized below:

A considerable expansion of effort in the planning and implementation of major clinical trials in hypertension and in a multiple risk factor intervention trial for the prevention of coronary heart disease has made increased demands on professional staff of the Therapeutic Evaluations Branch and the Biometrics Research Branch. These new programs will require further professional staff to maintain the level of professional participation and supervision considered essential to achieve effective implementation of these trials at minimum realistic costs.

The conduct of large population epidemiological studies and multi-center clinical trials like the Coronary Drug Project provides a base of administrative and professional experience for these new clinical trials, however, the time demands of such complex programs cannot be absorbed within the present number of personnel.

1. The Hypertension Detection and Follow-up Program has acquired sufficient planning and pilot experience within 9 initial communities to confirm expectations for successful implementation of a formal intervention trial within total defined community populations.

The purpose of this Hypertension Detection Follow-up Program which will seek the participation of approximately 10,500 individuals between the ages of 30-69, is to determine the efficacy of anti-hypertensive therapy in the whole spectrum of persons found to have elevated blood pressure in community based populations. Women, younger adults and persons without target organ disease, but with persistent elevation of diastolic blood pressure of $\geq$95 mm. Hg. will also be included.

Randomization to a "Stepped Care" or to "Regular Care" will be made and a follow-up of 5 years is planned to determine the extent of reduction of total mortality as well as morbidity from myocardial infarction, stroke, hypertensive heart disease, congestive heart failure, progressive hypertension, renal failure and other laboratory measurements.

The Protocol for Phase II has been reviewed and approved by the Policy Board of this program. Selection of 5 additional clinical groups has been made on an open competition in response to an RFP. This will complete the 15 clinical community centers considered needed to acquire the 10,500 participants with elevated blood pressure for the determination of efficacy of anti-hypertensive therapy within the general population.

The prevalence of elevated blood pressure of $\geq$95 mm. Hg. diastolic within the initial group of communities ranged from 10.5% in an Italian-American community to 28% in a black community. An average prevalence for the combined community populations should be near the 15% level found in the National Health Survey.

2. A Multiple Risk Factor Intervention Trial for the primary prevention of myocardial infarction and premature death from coronary heart disease has progressed through the initial process of open invitation by RFP to interested investigators, primary review of responses by a Special Review Panel consisting of members of the Therapeutic Evaluations Committee and members of the Epidemiology and Biometry Advisory Committee supplemented by further ad hoc reviewers with expertise in hypertension, nutrition, biostatistics and behavioral science.

Ten of the 23 proposals for participation in the clinical trial were recommended by the primary review committee and concurred in by the NHLI secondary review. Only 7 will be funded initially to form a nucleus of a planning group of investigators to develop the detailed protocol and carry out pilot testing of the standard protocol before expansion to a total of 20 centers to achieve enrollment of a planned 12,000 men between the ages of 40-59 who are ranked in the upper 15% of risk of developing early myocardial infarction on the basis of the level of their blood cholesterol, blood pressure or amount of cigarettes smoked.

The objective of this clinical trial is to determine the degree to which myocardial infarction and death from coronary heart disease can be reduced among high risk men with combinations of these risk factors in a randomized clinical intervention trial planned to last for 6 years. A target goal of 10% reduction of cholesterol by diet, 10 mm. Hg. reduction or normalization of diastolic blood pressure by anti-hypertensive drugs and a 50% reduction of amount smoked should result in a significant reduction in the incidence of myocardial infarction or of deaths from coronary heart disease in the intensively treated group as compared with the control group maintained under regular care over the period of this 6 year primary prevention trial.

3. The Coronary Drug Project, a secondary prevention randomized clinical trial of four lipid altering drugs to determine their efficacy in reducing mortality and recurrences of myocardial infarction has now completed more than 3 years of average patient follow-up. Continued close monitoring of morbidity and mortality revealed an unfavorable trend for the high risk group allocated to the dextrothyroxine regimen. A recommendation for a change of protocol by the Data and Safety Monitoring Committee was reviewed and approved by the Policy Board and Steering Committee resulting in removal of this drug from the study. Although DT_4 patients maintained a lowered cholesterol and triglyceride level, the increasing trend of mortality made it undesirable to continue patients any longer on this lipid lowering drug. Publication of the findings leading to this decision was made in the May 15, 1972 issue of Journal of the American Medical Association.

The other study regimens still being tested are: conjugated equine estrogens 2.5 mm/day, nicotinic acid 3.0 gm/day, clofibrate 1.8 gm/day and a placebo control group.

Analysis of mortality and recurrence rates from myocardial infarction in the placebo control group has revealed a number of clinical and electrocardiographic characteristics which are highly predictive for risk of recurrence of MI and death from coronary heart disease. Such knowledge should be of value in future efforts to develop or apply management regimens for patients who have survived their initial attack of myocardial infarction.

4. In addition to the biostatistical assistance and consultation to the Hypertension, Multiple Risk Factor and Coronary Drug Project, the Biometrics Research Branch staff under Dr. Max Halperin, have provided assistance in the Urokinase-Streptokinase Pulmonary Embolism Trial, the Sickle Cell Anemia

Trials, and the Intramural Type II Coronary Intervention Trial. The scope of these activities requires more formal organization and supervision of the increasing responsibilities in clinical trials. Recruitment of an additional senior professional to oversee these responsibilities is urgently needed.

5. Biometrics staff participation and consultation with epidemiological studies continued on an active basis under Mr. Tavia Gordon, Supervisory Statistician and his staff. The data from these epidemiological studies are providing increasing documentation of the differences in incidence of myocardial infarction between the populations under study in Puerto Rico, Honolulu-Hiroshima, Yugoslavia and Framingham. Systematic analysis of the strength of contribution of various risk factors is being conducted in cooperation with the principal investigators of these epidemiological studies. Considerable clarification of the importance of a variety of factors contributing to the development of angina pectoris, myocardial infarction, sudden death and death from coronary heart disease is resulting from these studies.

6. The Framingham Study continued active production of further reports of findings from the follow-up data from the study population of 5,192 persons who have been studied over a 16 year period. Detailed individual publications have been produced on findings related to coronary heart disease, congestive heart failure, stroke due to brain infarction, intermittent claudication, sudden death and on unrecognized or silent myocardial infarction.

A significant finding of the Framingham Study has been the demonstration that the same factors of elevated systolic or diastolic blood pressure, serum cholesterol, glucose intolerance, cigarette smoking and LVH on ECG are of importance not only for coronary heart disease but also of importance in brain infarction and intermittent claudication of atherosclerotic origin.

Data for the 18 years of follow-up have now been entered on computer tape and will allow further extension of analysis for the less common types of events. The 18 year data have accumulated the following number of events: 674 cases of CHD, 192 cases of CHF, 193 cases of CVA (108 of ABI), 253 cases ofIC and 1001 deaths. This has added 235 cardiovascular events in the 2 year interval from the 16 year follow-up experience.

7. The Framingham Offspring Study supported under a separate contract for laboratory and clinical examinations has received good acceptance from the population. Some 1200 offspring were examined according to a study protocol to make possible exploration of familial and genetic associations between parents and their offspring in relation to risk factors, particularly the lipid fractions.

A unique aspect of this study will be the production of clinical and laboratory measurements on offspring at ages close to that of their parents when they entered the study 20 years earlier.

8. Twin studies under a core standardized protocol have been extended to 4 geographical areas where access to known sets of twins identified by the roster developed by the National Academy of Sciences Follow-up Agency.

From the total of 6 areas involved in this cooperative study, 400 pairs of male twins aged 25-55 have now been examined. Preliminary results indicate major genetic determinants of the observed variability in height, weight and serum cholesterol levels, moderate genetic effects on blood pressure and virtually no genetic component for the variability in serum triglycerides.

9. The Honolulu-Hiroshima-San Francisco study of the epidemiology of coronary heart disease and stroke among Japanese-American men and men in the Atomic Bomb Casualty Commission study aged 45-64 has continued to increase the number of clinical events available for analysis purposes.

The low incidence of myocardial infarction in the Japanese male population of the ABCC study was confirmed. The comparative annual rates between Hiroshima, Honolulu and Framingham using the Framingham incidence as a scale equal to 100 would rank Honolulu incidence at 40 and a Hiroshima incidence of 20 or one-fifth of that found in Framingham.

Preliminary analysis based on 101 incidence cases in the Honolulu study reveal significant differences in blood pressure and in measures of adiposity such as skinfold measurements and casual blood cholesterol and triglyceride levels. Differences between the Issei and Nisei exist even when adjusted for levels of known risk factors. The higher incidence is present among the Nisei.

The further cycle of follow-up should provide sufficient cases of stroke as well as of coronary heart disease to extend these epidemiological observations in relation to a variety of other measured characteristics.

10. The Puerto Rico study of coronary heart disease completed the re-examination and mortality follow-up for incidence of myocardial infarction on 8301 men aged 45-64 with confirmation of the low myocardial infarction incidence within this population. A provisional incidence which is 38% of that found for men of the same age in the Framingham study has been established. This is confirmatory of the low mortality which previously attracted attention to the epidemiological interest in this population.

Comparison of differences in characteristics between urban and rural men aged 45-64 has revealed significant differences in cholesterol, triglyceride, glucose levels, relative weight, physical activity, per cent calories from fat and per cent of carbohydrate as starch. Relative weight was the most significant variable in explaining urban-rural differences in serum glyceride and cholesterol levels.

11. Collaborative epidemiological studies are being continued with investigators in Israel and Yugoslavia. Five year incidence data relating to a population of 10,232 men age 40 and over are receiving extensive analysis for findings relating to ischemic heart disease, diabetes, hypertension and peripheral vascular disease. The population cohort of 11,121 men aged 35-64 in two Yugoslavian communities is also being followed through examination procedures made comparable to those in Framingham. An incidence of myocardial infarction only 19% of the level found for age 45-64 men in Framingham has been established. The factors related to this extremely low incidence are under continuing investigation supported by P.L. 480 counterpart currencies as has been done with the Israel study.

12. Nutritional studies incorporated into most of the larger epidemiological projects are producing data about the dietary intake of these free living populations. Serum cholesterol levels show a significant positive regression with per cent of calories from saturated fat and significant negative regression with per cent of calories from carbohydrate within each of the three Japanese populations under study. However, only a small per cent of the variation in cholesterol levels are explained by these dietary variables. Factors which promote obesity are strongly related to population triglyceride levels and less strongly to cholesterol levels. Much greater clarification of the role of dietary factors as determinants of lipids within free living populations is needed before undertaking national recommendations relating to modifications of food products or of diet patterns.

13. Development and evaluation of nutrition education programs for the dietary management of hyperlipidemia is an important area related to the planning of the Multiple Risk Factor Clinical Trial and also for more general purposes.

Two contracts from a group of 21 responses to invitations for undertaking research on this problem have been awarded. One of these contracts will develop and test 4 educational methods in populations of different socio-economic background. The other contract has a greater emphasis on characterizing the type of educational technique to which a given individual best responds and applying this educational approach in the given patient. In general, it seems possible to develop more effective educational and motivational approaches in this important area which affects lifetime patterns of food preference yet achieve a desired dietary prescription.

14. The cardiorespiratory research activities have taken on a new emphasis and new projects have begun under the supervision of Dr. Albert Roberts. Special emphasis was given to the exploration of the role of AAT deficiency in obstructive pulmonary disease, particularly in the Honolulu study and within the Yugoslavia project. Phenotyping techniques have been established and have been introduced into formal protocols of study in both of these populations.

SUMMARY

In general, the increasing scope of activities in clinical trials has been undertaken without additional staff. The increasing NIH emphasis to provide closer interrelationship between investigators funded to undertake cooperative clinical trials and Institute professional scientists or scientist administrators requires increased positions.

Relief from the position restrictions is urgently needed to undertake the committed program responsibilities. Lack of positions to bring on additional personnel is by far the dominant problem which will impair the quality of work within the programs unless these restrictions are modified.

PHS-NIH
July 1, 1971 through June 30, 1972
National Heart and Lung Institute
Clinical Applications
Biometrics Research Branch

In contrast with the last fiscal year, during which personnel losses were substantial, there have been no personnel losses during the current fiscal year while three new members have been added to the staff as replacements. New professional staff members are Dr. Frantz Ashley and Mr. Daniel McGee in Mr. Gordon's work area, including Framingham and allied studies, and Mrs. Marian Fisher in the statistical consulting group under the supervision of Dr. Friedewald. Dr. Ashley is a Ph.D. in Mathematics with additional extensive graduate statistical training at Stanford and came to us after a stint as statistician with the Atomic Bomb Casualty Commission. Since joining us in Sept. 1971, Ashley has been providing statistical assistance to the α-1 anti-trypsin study underway in Honolulu and has been engaged in the analysis of respiratory function data from Framingham. In addition, he has been attempting to develop appropriate statistical models for the analysis of relationships between concurrent changes in different measurements (e.g. cholesterol changes over a period of time and concurrent weight changes).

This difficult issue has not yet been successfully resolved and an interim procedure suggested by W. C. Blackwelder and Max Halperin is currently being used in such analyses. Mr. McGee, who joined us in April 1972, has an M.S. in Mathematics and joined us from a position as a college mathematics instructor and is assisting in providing programming and analytical services in connection with various field epidemiology studies.

Mrs. Marian Fisher joined our statistics consulting group in about Sept. 1971, after completion of substantially all requirements for the Ph.D. in Mathematical Statistics at George Washington University— it is anticipated she will receive her degree in August 1972. Some of her efforts have been devoted to theoretical and numerical work relating to problems of appropriateness of various data analyses which the branch has had to review. She has also recently become involved at the request of Dr. Tom Chalmers in the analysis of a complex body of data from the Boston City Hospital Registry on the course of patients in Fulminant Hepatic Failure. In addition, some of her time is spent in supervising and directing the efforts of DCRT personnel providing data processing capability for the intramural Type II Coronary Intervention Study.

Mention should be made that shortly before the close of last fiscal year but after preparation of the annual report, Mrs. Myrna Miles joined the branch as a secretary for Mr. Gordon and his group.

Other personnel changes of interest include the return of Joel Verter to our consulting group after two years of graduate study in statistics at the University of North Carolina under PHS sponsorship and the departure of W. C. Blackwelder for further training at the same institution, also under PHS auspices.

As a final personnel note on special recognition to members of the branch during the fiscal year, Max Halperin was elected a member of the International Statistical Institute, an international organization with a quite restricted membership, and Tavia Gordon was named a Fellow of the American Statistical Association in recognition of his statistical contributions to Heart Disease epidemiology as well as his work in demography and health surveys.

The activities of our coordinating center for the ongoing USPET (Urokinase-Streptokinase Pulmonary Embolism Trial) under the supervision of Christine Cole has included in addition a considerable effort related to the preparation of a final report for the UPET (Urokinase Pulmonary Embolism Trial) and serving as coordinating center for the pilot phase of SUMIT (Streptokinase-Urokinase Myocardial Infarction Trial).

In these areas the activity has included final data analyses, processing of incoming data, forms design, preparation of randomization schedules, preparation of mouthly progress reports, and periodic reports containing data tabulations and analyses needed by the leadership and committees of the studies. The UPET activity has now terminated while the SUMIT work is expected to phase out during the fall of 1972 at which time it is anticipated a coordinating center outside of NHLI will be in operation for the expected operational phase of SUMIT. The USPET coordinating activity is currently anticipated to start phasing out early in the next calendar year since present plans call for termination of patient intake by the end of 1972; plans for future activities of this group are now under active consideration with the strongest likelihood being that these personnel will be utilized in some phase of our expanding clinical trial activities. James Neaton of the coordinating center has also been working with Fred Ederer of the National Eye Institute on retrospective analyses of some data investigating correlation of aspirin consumption with the development of thromboembolism; this work was initiated when Ederer was with the NHLI.

Mr. Gordon and his group continue in the analyses of data from the Framingham study in cooperation with Dr. Kannel's group and are continuing to provide statistical consultation and services for Puerto Rico, Honolulu and Yugoslavia attempting to coordinate the studies so as to achieve comparability and investigating the extent to which available findings in the different studies agree. Some interesting early findings are emerging some of which are worth a brief description.

Thus, the first round CHD incidence data for Honolulu is now in hand and is being analyzed. Mr. Gordon and Mrs. Schiffman have now explored the data extensively with Dr. Kagan and find that the same risk factors apply here as in Framingham. The four major novelties are a very strong role of relative weight in the development of CHD, a significant independent role for uric acid, a lower incidence of CHD among Japanese born in Japan than among these born in Hawaii and a significant association of CHD incidence with a family history of cardiovascular death. All these findings appear to be important irrespective of whether other risk factors are considered.

Puerto Rico first round CHD incidence is not yet ready for analysis but preliminary data are now available for interstudy comparisons. Electrocardiographic findings of definite MI are half as common in rural as in urban groups. Urban Puerto Ricans and Honolulu Japanese have about the same prevalence of this finding and for both, the prevalence is only half that in Framingham. A careful incidence comparison between Honolulu and Framingham indicates that the incidence of MI or CHD death in Honolulu Japanese is less than half that in Framingham and that this disparity holds even when differences in risk factors are accounted for. What is more, case fatality rates are lower in the Honolulu Japanese than in Framingham.

Other efforts in Mr. Gordon's area include those of Thomas Thom who, in addition to continuing to routinely provide new data on cardiovascular morbidity and mortality for purposes of program planning, provided staff assistance to the ad hoc Task Force on Atherosclerosis. He has also been devising and negotiating a followback study to provide much needed information on the circumstances surrounding deaths from cardiovascular and respiratory diseases. Also to be noted is Marthana Hjortland's work in completing a thorough analysis of some data on the diets of twins, utilizing data from Dr. Feinleib's twin studies. This work has also provided the basis for her doctoral thesis in Biostatistics; she expects to receive her degree this summer.

The work of Mr. Rogot's group on the migrant study continued during the year. In particular in the mortality phase of the study statistical analysis of 5 years (1963-67) of migrant deaths is underway. It is anticipated that the statistical analysis will soon be completed. The writing of the final report is underway.

Mr. Rogot is continuing work on the V.A. study of the relationship of the use of Tobacco to Health. The files have been updated to include all known deaths from 1954 through 1969. The statistical analysis is underway. The analysis will be confined to deaths from all causes. It is anticipated that the analysis will be completed soon and a monograph prepared for publication. This will, in large measure, terminate efforts on this study.

In addition, Mr. Rogot, taking advantage of the death certificates obtained primarily for Migrant Study needs, has completed a study of mortality data from Chicago, Illinois for 1967, to relate climatological factors to mortality from cardiovascular disease and respiratory disease. Of particular interest was a study of the association between coronary deaths and snowfall which could not be determined from an earlier small similar study of mortality in Memphis, Tennessee. The results for Chicago indicated (a) that there is an inverse linear relationship between number of CHD deaths per day and average temperature on day of death and (b) after adjustment for temperature, there is a significantly larger number of CHD deaths on days with snowfall than on days with no snowfall.

Mr. Rogot has now begun a similar study of mortality and weather for NYC for 1967.

It is apparent from the above that some re-direction of effort of Mr. Rogot's group will probably be necessary after the middle of next fiscal year. So far various alternatives have been under discussion with no conclusion as yet.

The statistical consulting group under William Friedewald, in addition to regular consulting activity, which will be summarized later, has tried to answer new needs in the clinical trials area. Aside from participation by Max Halperin and William Friedewald in ongoing clinical trials under the aegis of the Associate Director for Clinical Applications as statistical liaison and members of various committees there have been a number of other needs we have tried to meet, both in and out of the Clinical Applications area. These include statistical planning for the proposed Multiple Risk Factor Trial to modify blood pressure, cholesterol and smoking habits by Max Halperin and William Friedewald, statistical planning and participation in committee work of the Sickle Cell Anemia Trial by William Friedewald and Joel Verter, a similar effort for the proposed Myocardial Infarction Trial by James Ware and Max Halperin (including construction of a sequential procedure allowing possible early termination of the trial), provision of statistical support for the intramural Type II Coronary Interventions Trial by, as previously noted, Marian Fisher and, as well, William Friedewald. Other activities in the clinical trials area will be noted in the description of outside activities of Branch personnel later in this report.

James Ware and Max Halperin have been continuing their work aimed at deriving statistical procedures which would allow valid early termination of clinical trials whatever the nature of the appropriate conclusions. Most of the necessary mathematical analysis has been accomplished and currently alternative statistical tests are being compared in terms of their early stopping properties and their sensitivity to detecting treatment differences; it is not yet clear that one can have both good early stopping properties and good sensitivity. It is hoped to have this resolved within a short time. There are many other problems in this area which we hope to investigate. A paper for publication is under preparation as well as an invited presentation of this work at the 1972 meetings of the American Statistical Association. Marian Fisher has been spending some of her effort in investigation of new methods for analysis of complex tables of cross classified relative frequencies which is related to her dissertation and will also afford us further useful methods of data analysis. Joel Verter, at the request of Dr. Feinleib, did a brief numerical and theoretical investigation of various methods of estimating certain correlations of interest in twin studies, to ascertain which of several methods was the most accurate. It is believed the results are of interest to workers in genetics and a short paper will be prepared for publication.

As in past years, a book seminar has been carried on in both the Biometrics Research Branch and the Epidemiology Branch. This year's topic was non-parametric statistics. In addition, James Ware in cooperation with Dr. Schlesselman of NICHHD organized an NIH Mathematical Statistics and Probability Seminar giving us the benefit of exposure to the ideas of a number of distinguished statisticians from NIH, other governmental institutions, industry and universities.

The remainder of this narrative gives a number of examples of the consultation activity of the Branch and a listing of publications and other activities. Publications listed are only those not listed in year end reports of other NIH components by the senior author.

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Consultation

William Friedewald consulted with:

-Dr. Chester Clark, NHLI-C, on design aspects and sample size estimates for a coronary artery by-pass study.

-Dr. Barbara Roberts, NHLI-LM, on the utilization for screening purposes of percentage distributions of serum cholesterol and triglyceride as estimated from various epidemiological studies.

-Dr. Robert Levy, NHLI-LM, Lipid Research Clinics Intervention Committee on various aspects of trial design and sample size estimates.

Morton Raff consulted with:

-Dr. Robert Goldstein, NHLI-C, on analysis of data comparing the effects of various drugs on the relationship between contractility of heart muscle and heart rate in dogs.

-Drs. Leonard Grauer and John Hirshfeld, NHLI-C, on analysis of data concerning the effect of norepinephrine on the concentration of cyclic AMP in the papillary muscles of cats.

-Dr. Joseph Handler, NHLI-LKEM, on analysis of data estimating and comparing the effects of certain hormones on the permeability properties of the urinary bladder of the toad.

-Dr. Harriet Maling, NHLI-LCP, on a number of designs and analyses in bioassay problems involving estimating and comparing the effects of various drugs on inflammation and its inhibition, salivation, and temperature responses in mice and rats.

-Dr. Jay Shapiro, Washington Hospital Center, on analysis of data on race and sex differences in the relation of density of bone marrow to bone width, in a study of osteoporosis.

-Dr. Eldon Smith, NHLI-C, on the analysis of data relating to the effect of changes in heart rate and blood pressure on myocardial ischemia in dogs whose coronary arteries were partly occluded.

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Joel Verter consulted with:

-Mr. Tavia Gordon and Dr. Manning Feinleib-NHLI-EB, on the application of some recently developed multivariate analysis techniques to various sets of epidemiological data and on methods for the appropriate application of Framingham Risk functions to other populations.

James Ware consulted with:

-Dr. John Gill, NHLI-CE,on comparison of estimates of fractional catabolic rates of albumin in normal subjects to those for hypoalbuminemic patients to test the hypothesis that hypoalbuminemia is sometimes attributable to a high rate of albumin catabolism.

-Dr. James Gross, NHLI-CE, to analyze data on kidney function in the right and left kidneys of dogs bilaterally renal catheterized and receiving prostoglandin in one kidney. The objective was to measure the effects of prostoglandin on kidney function.

William Friedewald and Joel Verter consulted with:

-Dr. John Kattwinkle and Dr. Lynn Taussig, NIAMO-PM, on the design of forms for a scoring system for cystic fibrosis (CF) patients, on the analysis of data collected on these forms, and on the establishment of normal limits for several serum enzyme levels.

William Friedewald and Marian Fisher consulted with:

-Mrs. Susan Foster R.N., on data analyses of a pilot study to evaluate a nurse's ability to alleviate patient anxiety prior to heart surgery.

Morton Raff and William Friedewald consulted with:

-Dr. Blair Bowers, NHLI-LB, on a method of estimating the rate of surface deletion in pinocytosis from a set of 2-dimensional electron micrographs.

-Drs. Robert Henkin and Paul Schechter, NHLI-ET, on design and analysis of a doubleblind study of the effect of zinc ion on disorders in the sense of taste. They have been listed as co-authors of a resultant paper, in press.

-Dr. David Horwitz, NHLI-ET, in the analyses of data on the relation of age, sex, race, and blood pressure to levels of the enzyme dopamine beta-hydroxylase (DBH).

-Dr. Friedhelm Lamprecht, NIMH-LCS, on the analysis of data on the relation between blood pressure and the enzyme DBH in normal blood donors.

Morton Raff and Joel Verter consulted with:

-Drs. Michael Beaven, Zdenka Horakova, and Floyd Atkins, NHLI-ET, on an efficient computing procedure for the assay of histamine by a double isotope method.

-Dr. D. Luke Glancy, NHLI-C, and Dr. David Melvin, NHLI-SURG, on analysis of data from a study of the effect of various valve replacements on several qualitative and quantitative measures of a patient's condition.

James Ware and Morton Raff consulted with:

-Dr. Harriet Maling, NHLI-LCP on analysis of data measuring the effect of caffeine on physical activity levels in rats.

-Dr. Robert Bowman, NHLI-LTD on a mathematical analysis of a model of acceleration in an apparatus used for centrifuging.

-Dr. Paul Tecklenberg, NHLI-SURG on analysis of data from EEG's of digitalized patients to establish a criterion for digitalis toxicity.

James Ware, Morton Raff and William Friedewald consulted with:

-Dr. Richard Karsh, NHLI-C, on analyses of data measuring the effect of atropine on the arrhythmic consequences of induced acute myocardial infarction in dogs.

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Publications:

Walsh, P.N., Greenspan, R.G., Simon, M., Simon, A.L., Hyers, T.M., Woosley, P.C., Cole, C.M.: An Angiographic Severity Index for Pulmonary Embolism. To appear, Supplement to Circulation.

Friedewald, W.T., Levy, R.I., Fredrickson, D.S.: Estimation of Plasma Low Density Lipoprotein Cholesterol Concentration Without Use of the Preparative Ultracentrifuge. Clinical Chemistry. In press.

Friedewald, W.T., Halperin, M.: Clofibrate in Ischemic Heart Disease, Editorial. Annals of Internal Medicine, 76: 821-823, 1972.

Halperin, M., and Gurian, J.: Estimation of Slope in Straight Line Regression When Both Variables are Subject to Error. Journal of the American Statistical Association. 66: 587-589, 1971.

*Ware, James H.: Fitting Straight Lines When Both Variables are Subject to Error and the Ranks of the Means are Known. Journal of the American Statistical Association. (to appear Dec 72).

*Most of this work done elsewhere.

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Unpublished Papers and Talks

Kullback, S. and Fisher, M.: Partitioning Second-Order Interaction; a paper submitted for publication to Applied Statistics.

Kullback, S. and Fisher, M.: On Multivariate Logit Analyses; a paper submitted for publication to Biometrics.

Gordon, T.: Obesity and Cardiovascular Disease; a talk given at the Inter-American Congress of Cardiology, April, 1972.

Halperin, M.: Early Termination in Clinical Trials; a talk given at Summer Seminar on Data Analysis, Colorado State University, July, 1971.

Rogot, E.: Association of Cardiovascular Mortality with Weather; an invited paper presented at a Symposium on Air-Conditioning, Climatology and Health at the Annual Convention of ASHRAE (American Society of Heating, Refrigerating and Air-Conditioning Engineers in Washington, D. C., August 22, 1971). This paper is being considered for publication in an ASHRAE Symposium Bulletin.

Rogot, E.: Associations of Coronary Mortality with Weather; an invited talk given at a Seminar in Environmental Physiology at the John B. Pierce Foundation Laboratory, New Haven, Conn., November 15, 1971.

Ware, James H.: A Survey of Recent Work Toward Early Termination of Clinical Trials; an invited talk given at the Eastern Regional Meeting of the Institute of Mathematical Statistics, April 19, 1972.

Ware, James H.: Early Stopping in a Censored Wilcoxon Two Sample Test; invited seminars given at Stanford University, The University of Washington and Carnegie-Mellon University, during the months of October and November, 1971.

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Participation in Outside Committees and Organizations

Christine Cole:

-served as a member of the Urokinase-Pulmonary Embolism Trial (UPET) and the Urokinase, Streptokinase-Pulmonary Embolism Trial (USPET) Advisory Committee for Statistical Analysis

William Friedewald:

-served as a member of the Data and Safety Monitoring Committee and the Natural History Committee of the Coronary Drug Project.

-served as a member of the Urokinase-Streptokinase-Pulmonary Embolism Trial's Advisory Committee for Statistical Analysis.

-served as a member of the Governing Board of the Sickle Cell Anemia Trial.

-served as a member of the Advisory Committee for three trials being done under contract to the Blood Resources Branch; these are trials of Hyperimmune γ-Globulin in Acute Fulminant Hepatitis, in the prevention of hepatitis from accidental inoculations and in the prevention of hepatitis among patients and staff of Renal Dialysis Units.

-served as a member of the Data and Safety Monitoring Board of the intramural Type II Coronary Intervention Study.

-served as a member of an Ad Hoc Review Committee of a proposal to NIAID from the Navy to produce and evaluate antilymphocyte serum.

Tavia Gordon:

-served as a member of the Tripartite Japanese Study Steering Committee
-served on the AHA Pooling Project Committee.

Max Halperin:

-served as an Associate Editor of the Journal of the American Statistical Association.

-served on the Coronary Drug Project Steering Committee, Data Analysis and Safety Monitoring Committee, Natural History Committee, Resources Committee.

-served on the Hypertension Detection and Follow-up Program's Steering Committee, Design and Analysis Committee, Officers and Staff Committee.

-served on the USPET Advisory Committee for Statistical Analysis.

-served on the Committee on Fellows, Washington Statistical Society.

Morton Raff:

-served as a referee for the Journal of the American Statistical Association.

James Ware:

-served as a referee for the Journal of the American Statistical Association.

-served as a statistical advisor for the Streptokinase Urokinase Myocardial Infarction Trial.

Serial No. NHLI-BRB-1
1. Biometrics Research Branch
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Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Statistical Problems Related to the Cooperative Study of Drugs and Coronary Heart Disease

Previous Serial Number: Same

Principal Investigators: James Ware and Max Halperin

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.60
Professional:	.60
Others:	0

Project Description:

Objectives: To provide statistical methods for the analysis of long term clinical trials like the Coronary Drug Project, alternative to those so far proposed. A special focus of the project is an attempt to provide criteria allowing the conclusion, during the course of the trial, that on a purely statistical basis one or more treatments or placebo should be terminated. The basis for such a conclusion would be that a statistically significant result for particular treatment placebo comparisons at the end of the trial is very likely or contrariwise very unlikely. An aspect of the method being considered differentiating it from others is that the decision to terminate a treatment or the placebo is based upon both the accumulated data and projections of what can reasonably be expected by the end of the trial.

Methods Employed: The basic ideas and methodologies involved in this problem are not new. In a situation where it can be argued that every individual will suffer the event of interest and the trial can continue until this happens, the question of early stopping has been investigated by other workers. They have demonstrated that marked savings in the total number of events required (and thus time) can be achieved. Our investigation is an attempt to generalize the procedure to a setting in which, even if the trial continues to the end, only a fraction of the individuals at risk will have the event. Methods of classical mathematics and theoretical statistics are the essential tools.

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Major Findings: For the case of comparison of two cohorts and assuming an event certain to occur eventually, e.g. death, we have formulated an experimental design for a clinical trial in which the trial is terminated when a fixed percentage of events have occurred in either. With this formulation, we have shown that early stopping can be anticipated in a wide variety of circumstances. The criterion for early stopping has been explicitly described and the appropriate statistical distribution theory has been developed. The distribution theory for the number of events required before the trial can be terminated has also been derived, as well as the distribution theory for the power of the procedure to detect differences between the survival distributions of the treatment and placebo groups. Since these results were based upon large sample size arguments, Monte Carlo studies were employed to insure that these results can be applied for sample sizes of interest at NHLI.

Significance to Bio-Medical Research and the Program of the Institute: It is hoped that this research will result in methodology which will increase the ability of statisticians to detect situations in which accumulating data justifies the early termination of clinical trials. From both the economical and ethical standpoints, earliest possible termination of clinical trials will significantly contribute to the effectiveness of the clinical trials conducted at NIH and elsewhere.

Proposed Course: Work is currently focused on consideration of several competitive methods of data analysis in an effort to determine the relationship between early stopping and sensitivity to treatment-placebo differences. The results of this investigation and the earlier findings will be reported in an invited paper at the annual meeting of the American Statistical Association on August 14, 1972, and submitted for publication to the Journal of the American Statistical Association.

This research has suggested new approaches to the problem of early termination of clinical trials and further research will explore these possibilities for improved capability to terminate clinical trials early. There is also a need for comparative studies to identify the strengths and weaknesses of the growing collection of methodologies for early termination of clinical trials.

Serial No. NHLI-BRB-2
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Cardiovascular and Respiratory Disease Among British and Norwegian Migrants in the United States

Previous Serial Number: Same

Prinicpal Investigator: Professor Donald D. Reid, London School of Hygiene and Tropical Medicine

Other Investigators: Eugene Rogot, NHLI; Charles E. Sydenstricker, NHLI; Jerome Cornfield, University of Pittsburgh; William Haenszel, NCI; Dr. Peter Lambert, London School of Hygiene and Tropical Medicine; Dr. Einar Pedersen, Dr. Tjorborn Mork, Norwegian Cancer Registry

Cooperating Units: Bureau of the Census; Department of Commerce; National Cancer Institute; National Center for Health Statistics; University of Pittsburgh; London School of Hygiene and Tropical Medicine General Register Office, England, Wales, and Scotland; Norwegian Cancer Registry; Central Bureau of Statistics, Norway

Man Years:

Total:	.9
Professional:	.5
Others:	.4

Project Description:

Objectives: To determine morbidity and mortality from chronic respiratory and cardiovascular diseases among British and Norwegian migrants in the United States and to compare this with corresponding data for native born residents of Great Britain, Norway and the United States. This is part of an investigation to determine reasons for the difference in the incidence of these diseases in the three countries.

Methods Employed: Information on morbidity from cardiovascular and chronic respiratory diseases, residence history, occupation, use of tobacco, and other environmental variables has been collected by two-stage mail questionnaires (a health screen, and a detailed health query) from a sample of 50,000 British and Norwegian migrants in the United States and from a sample of 20,000 U.S. native born. Death certificates for all deaths of British born persons in 1963 and 1964 and for all deaths of Norwegian-born persons in 1963-66 in the twelve states sampled for the morbidity survey,

and for a 2% sample of deaths of the native born in 1963-64 have been secured from the National Vital Statistics Division. Personal and environmental data about the deceased have been obtained by mail questionnaire from the informant listed on the death certificate; diagnostic data and the nature of evidence supporting them have been obtained from the medical certifier of the death.

Corresponding morbidity studies in Great Britain and Norway have been carried out on the siblings of the migrants and on representative samples of the resident native population. A sample of death certificates in Great Britain has been secured and questionnaires have been sent to a subsample of medical certifiers.

Since much of the information collected in the mortality phase is similar to that obtained in the morbidity phase, death rates are being analyzed with respect to a number of factors. In this way, deaths in the entire migrant population rather than only those of persons included in the morbidity sample are being used. This method of analysis is being carried out for 1963 and 1964 deaths for the British and for 1963-66 deaths for the Norwegians and will include about 13,000 British, 6,700 Norwegians and 15,000 native-born deaths.

A much more detailed mortality analysis is underway for the migrant groups. Under this plan, persons queried in 1962 are considered as cohorts who may be followed for X years with survivorship experience to be measured. Since detailed information is available on cardiorespiratory symptoms, smoking, occupation, income, age at migration and many other factors from the morbidity survey in 1962, cohorts may be distinguished on the basis of these characteristics and analyzed in a prospective fashion. With sufficient numbers of deaths the cohort study will prove especially valuable in furnishing data on probabilities of death by cause for the migrant groups. It is now planned to collect copies of death certificates for the migrants for a 5-year period. These will be matched against the morbidity survey listings.

Major Findings: Preliminary findings of the morbidity survey of British and Norwegian migrants to the U.S. and U.S. natives were published earlier (NCI Monograph No. 19, January 1966). These included (1) prevalence of symptoms of chronic respiratory disease which is no higher among British migrants than among U.S. natives, in contrast with the much higher prevalence in Britain; and (2) prevalence of symptoms of angina and myocardial infarction which is lower among British migrants than among U.S. natives, in accord with mortality differentials between the two countries.

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In Britain, selected findings of their morbidity survey have now been published (Lambert, P. M., and Reid, D. D.: Bronchitis in Britain: smoking and air pollution. Lancet, 1970). The results were summarized as follows:

A postal survey of the prevalence of respiratory symptoms has been carried out in a large sample of the British population. Analysis of the 9,975 replies from men and women aged between 35 and 69 (74 percent of these presumed able to reply) showed satisfactory agreement with census and other data.

Increasing prevalence with aging and cigarette consumption has been confirmed. A male excess is seen among non-smokers as well as smokers. Urban-rural gradients are not explained by smoking differences alone. Symptoms prevalence rates rise with increasing levels of air pollution independently of cigarette consumption. Without cigarette smoking, local pollution seems to have little effect. In smokers, however, high levels of pollution are associated with more frequent respiratory symptoms. The frequency of more serious bronchitis increases most steeply with age among smokers in the more polluted districts.

In Norway, information on respiratory symptoms was collected by mail from a general population sample aged 35-74 and sibs of migrants to the United States. The 2 groups yielded similar findings and were combined for analysis. An excess symptom prevalence among smokers rising with amount smoked, similar to findings from other countries, was noted. Some regional variation not accompanied by important urban-rural differences in symptom prevalence was observed. Urban residence and a high rate of tobacco use did not interact to produce prevalence rates greater than expected from the separate contributions of these 2 factors. The consistency of the symptom prevalence information with Norwegian mortality data for respiratory diseases was noted.

In the U.S., findings related to the success of the morbidity questionnaire as an instrument in predicting death from cardiorespiratory disease have been published (Krueger, D. E., Rogot, E., Blackwelder, W. C., and Reid, D. D.: The predictive value of a postal questionnaire on cardiorespiratory symptoms. J. Chronic Dis. 23:411-421, 1970). These results were summarized as follows:

A two-year follow-up has been carried out on 1,201 deaths occurring among 38,249 British and Norwegian male and female migrants living in the United States who answered a postal questionnaire on cardiac and respiratory symptoms. Supplementary data were obtained from the physicians certifying death or from other sources. Those answering positively to questions used

to define syndromes of 'angina,''possible infarction,' 'persistent cough and phlegm' and 'chronic bronchitis,' were found to have higher risks of death in the 2-year period than those answering negatively; and the excess came largely from coronary heart disease in those defined as having either cardiovascular syndrome and from chronic non-specific lung disease in those with respiratory symptoms. The potential of this novel method of establishing relative prevalence of cardiorespiratory disease in different populations is discussed.

Work continues in the U.S. on the analysis of mortality data.

Significance to Bio-Medical Research and the Program of the Institute:

Data on multiple causes of death and on other diseases present in British migrant decedents will reveal whether chronic respiratory disease not apparent in official mortality statistics is more common in this group than in the U.S. native-born. The morbidity surveys in Britain and Norway will show the levels of prevalence of symptoms in those countries and identify environmental and personal characteristics related to the differences. Surveys of siblings of migrants may help explain the low prevalence of symptoms among migrants to the U.S. Differences in cardiovascular mortality between U.S.-born and migrant groups will be studied. The 5-year cohort study should permit a wide variety of mortality analyses of British and Norwegian migrants. Prospective studies relating cardiorespiratory symptoms, smoking, occupation, income, age-at-migration, and many other factors to cause of death are planned.

Proposed Course: In the United States the morbidity survey has been completed and preliminary findings have been published. Further analyses may be undertaken. The major emphasis however will be in completing the mortality phase of the study. Analyses are underway for 2-year British and 4-year Norwegian mortality rates. These will focus upon such factors as age-at-migration, year of migration, smoking and other factors. Also underway are: an evaluation of the diagnostic accuracy of causes of death as reported on the death certificate, an evaluation of the accuracy of personal information about the decedent as supplied by the death certificate informant, an examination into selected combinations of causes of death, and an examination of sudden CHD deaths.

All morbidity questionnaire respondents who died in the years 1963-1967 have been identified; these furnish us with 5 years (1963-67) of migrant cohort deaths. The statistical analysis of these data is underway.

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It is anticipated that the statistical analysis of the U.S. material will be completed soon and the results prepared for publication.

In Britain and Norway morbidity questionnaires have been secured from the siblings of migrants as well as from samples of the general populations. All data have been edited, and most have been transferred to magnetic tape. A sample of deaths in the general population of Britain has been secured and multiple-cause coded. In both countries respondents to the morbidity questionnaires who die are being identified and their death certificates are being secured.

Serial No. NHLI-BRB-3
1. Biometrics Research Branch
2.
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Individual Project Report
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Project Title: Epidemiologic Study of Coronary Atherosclerosis in Puerto Rico (This refers to statistical services provided by the Biometrics Research Branch only. See general description in Clinical Applications Section.)

Previous Serial Number: Same

Principal Investigators: Joyce Schiffman (Study Chief is Dr. Mario Garcia-Palmieri)

Man Years:

Total	.40
Professional:	.40
Other:	--

Project Description:

Objectives: To study the factors related to development of cardiovascular diseases in a population of middle-aged men where the death rate from coronary heart disease is about one-third that in the U.S. mainland population. The study has been planned to make use of the unusually high autopsy rate (50%) and to maximize the heterogeneity in mortality rates, diet and physical activity observed in preliminary surveys of rural and urban residents.

Methods Employed: Anticipating a response of 80% or better, the study area was defined to yield 4,000 mountain dwellers and 8,000 city dwellers for a sample of 10,000 split 1:2 rural-urban. All males born in the years 1900 through 1919 and residing in the defined mountain areas or in specified municipios in the San Juan metropolitan area were enumerated in a household canvass by the Puerto Rico Planning Board. The second examination was completed in August 1971 with a 91% response rate. A paper explaining urban-rural serum lipid differences has been presented; other papers analyzing Exam 1 data are underway. Incidence analyses are being planned. A limited third cycle has been started in conjunction with the Lipoprotein Project.

Routine surveillance of response rates, mortality rates, and CHD incidence is undertaken. In addition, we supply consultative and backup statistical services.

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Methods Employed:

Data processing procedures and programming have been worked out with the Medical Center Information Processing Division in San Juan. Periodically data from the project has been converted to tape compatible with the NIH computer system to allow for exploratory tabulations here.

Significance to Bio-Medical Research and the Program of the Institute:
See general description in Clinical Applications Section.

Major Findings:
See general description in Clinical Applications Section.

Proposed Course: The second round of examinations has been completed with a response rate of 91%. A limited third round of examinations in the municipios of Bayamon, Naranjito and Comerio was started in August 1971. The lipoprotein study is being done on a sample from these municipios. The laboratory started doing the lipoprotein samples in January 1972.

Serial No. NHLI-BRB-4
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Coordinating Center Operations for the Urokinase-Pulmonary Embolism Trial

Previous Serial Number: NHLI-BRB-6

Principal Investigator: Christine Cole

Other Investigators: Thomas Hyers, James Neaton

Cooperating Units: NHLI Program Office and Medical Liaison: Blood Resource Program, NHLI; New York University Medical Center: Central Laboratory, 14 clinician-investigators

Man Years:

Total:	1.80
Professional:	1.20
Other:	.60

Project Description:

Objectives: To provide coordinating services required for the effective administration of a controlled cooperative clinical trial. The objective of the study was to compare the effects of two methods of therapy on the resolution rate of pulmonary thromboemboli: a 12-hour infusion of urokinase followed by heparin vs. infusion of heparin only.

Methods Employed:

1. Consultation on study design, including such aspects as methods of organizing a personnel structure for decision making, delegation of authority, and the smooth operational functioning of the study; standardization of methodology, and definitions; choice, methods of evaluation and quantification of endpoints; methods to prevent bias in the evaluation and interpretation of results; uniformity of procedures of observation, measurement, and data collection.

2. Preparation of a protocol, manual of operations, and forms.

3. Preparation of randomization procedures; prevention of bias in treatment assignment.

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4. Planning and developing systems for automatic data processing, including:

a. manual edit procedures
b. punch card layouts for data and summary cards
c. coding procedures
d. computer edit procedures
e. tabulation plans
f. writing and de-bugging computer programs for tabulations and computations

5. Data processing:

a. manual edit
b. coding, punching, and verifying data
c. computer edit of data
d. data tabulation and computation

6. Preparation of periodic (monthly) progress reports containing data on patient screening and accession, information on problems encountered in implementing the protcol and how to deal with them, progress on pilot studies, schedules of meetings, etc. These reports were distributed to all participants.

7. Preparation of periodic confidential reports containing data and analyses of results on complications of treatment, morbidity, mortality, and results of radiographic and hemodynamic studies. These reports were distributed to the Policy Board and the Advisory Committee for Statistical Analysis.

Major Findings: Urokinase and subsequent heparin therapy, when compared to heparin therapy alone, significantly accelerated the resolution rate of pulmonary thromboemboli at 24 hours as shown by pulmonary angiograms, lung scans, and right-sided pressure measurements.

Course of Project: Planning for the study started in September 1967. An organizational structure was drawn up: Chairman, Policy Board, Steering Committee, Coordinating Center, Central Laboratory, various committees, subcommittees, and review panels. Coordinating Center personnel are represented on the Steering Committee, the Protocol Committee, the Committee for Standardization and Analysis of Data, on Subcommittees for Analysis of Pulmonary Angiogram, Pulmonary Photoscans and Hemodynamic Data, and Biochemical Data,

and on the Hemodynamic Data Analysis Panel. A protocol and manual of operations were prepared and approved by the Steering Committee and Policy Board. The study was approved by primary and secondary contract review boards.

In addition to the five institutions which participated in the planning in 1967-68, eight institutions joined the study in the fall of 1968, of which four later withdrew, and four more in the spring of 1969, so that a total of 14 institutions eventually participated.

Pilot studies were undertaken to develop methods for the analysis of angiographic, pulmonary photoscan and hemodynamic data, the results of which are being applied to the evaluation of the data from the study.

The shakedown phase of the study began in the summer of 1968, and the official phase in the fall. Through August 1970, over a 22-month period, 161 official study patients were accessioned. Pulmonary angiographs and pulmonary photoscans were reviewed and evaluated "blind" by independent panels. The quality of the films and of other data was generally high, inter-reader comparability of angiograms and lung scans good, and cooperation of participating groups excellent. Data were processed continuously and results tabulated periodically.

The study was terminated in August 1970, and a new phase, a comparison of three modalities, was started: 12-hour infusion of urokinase, 24-hour infusion of urokinase, and 24-hour infusion of streptokinase.

A preliminary report of the findings has been published in the Journal of the American Medical Association. The Coordinating Center prepared final tabulations for a detailed monograph to appear as a Supplement to Circulation. In addition to evaluating differences between the two treatments on the resolution rate of pulmonary thromboemboli, the monograph includes observations on many aspects of pulmonary embolism: the spectrum of clinical manifestations; sensitivity of laboratory and radiographic studies; interrelationships among clinical and laboratory findings with severity of embolic obstruction; and the natural history of treated pulmonary embolism.

Serial No. NHLI-BRB-5
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: A study of seasonal mortality in 1967 for Chicago, Illinois

Previous Serial Number: NHLI-BRB-7

Principal Investigator: Eugene Rogot

Other Investigator: Charles E. Sydenstricker

Man Years

Total:	.6
Professional:	.4
Other:	.2

Project Description:

Objectives: To study the relation of a number of climatological factors to mortality from cardiovascular disease, respiratory disease, and other diseases. In particular, to examine the association between coronary deaths and snowfall. Also to evaluate data on sudden deaths from coronary heart disease for seasonal patterns.

Methods Employed: Reels of microfilm of death certificates for 1967 in Illinois have been made available for use in the British-Norwegian migrant study. Multiple cause of death data has been coded from these microfilm reels for a total of 39,418 deaths occurring in Chicago in 1967. One advantage in using Chicago deaths is that multiple cause data are entered on these certificates routinely.

Information coded for each death includes residence (Chicago or other), age at death, race, sex, date of death, hour of death, I.S.C. 4-digit code for each cause of death up through six causes, and interval between onset and death for the immediate cause. In addition, daily climatological data for Chicago have been obtained for 1967 for maximum, minimum, and average temperature; total precipitation; snowfall and sleet; average and maximum wind speed; maximum and minimum relative humidity; and other variables.

Tabulations have been prepared to show variation of mortality from selected causes according to climatological variables, with deaths categorized by age, sex, and race.

Serial No. NHLI-BRB-5
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Major Findings: The weather variable most strongly associated with cardiovascular (CV) mortality was daily average temperature, which was inversely related to mortality from CV disease, whether or not respiratory disease was present. An inverse linear relationship was observed for temperature versus coronary heart disease (CHD) deaths but no clear-cut pattern was observed for temperature versus deaths from strokes, the pattern observed for CHD mortality and temperature held for males but not for females; further, patterns were similar for whites and nonwhites, and for ages under 65 and 65 and over. Sudden CHD deaths showed much the same inverse linear relationship to temperature as did other CHD deaths. After controlling for temperature positive associations were noted for CHD mortality and snowfall.

Significance to Bio-Medical Research and the Program of the Institutes:

A study of seasonal mortality patterns in a large northern city should be valuable in determining the generality of the relationships found in Memphis. It is believed that the use of multiple cause of death data from a large city to study seasonal patterns in mortality, and studies of sudden coronary deaths and of the possible association between coronary deaths and snowfall, are new.

Proposed Course: The statistical analysis has been completed. A paper entitled "Association of Cardiovascular Mortality with Weather" was presented at a Symposium on Air Conditioning, Climatology and Health at the 1971 annual convention of ASHRAE (American Society of Heating Refrigerating and Air-Conditioning Engineers). This paper is being considered for publication in an ASHRAE Symposium Bulletin.

A talk entitled "Associations of Coronary Mortality with Weather" was given at a seminar in environmental physiology at the John B. Pierce Foundation Laboratory in New Haven, Conn. The material for this presentation will be prepared for publication.

Serial No. NHLI-BRB-6
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Relationship of the Use of Tobacco to Health

Previous Serial Number: NHLI-BRB-9

Principal Investigator: Eugene Rogot

Other Investigators: Charles E. Sylenstricker

Cooperating Units: Department of Data Processing and the Veterans Benefit Office, Veterans Administration

Man Years:

Total:	1.0
Professional:	.8
Other:	.2

Project Description:

Objectives: To evaluate the relation of tobacco usage to subsequent mortality.

Methods Employed: Information concerning residence, occupation, and the use of tobacco has been collected from about 248,000 persons out of a total of 294,000 persons who held U.S. Government Life Insurance policies in December, 1953. As each person included in the study terminated a policy, the procedure was for the Biometrics Research Branch to be notified by the Veterans Administration. If the policy terminated as a result of death, the death certificate was to be obtained. If the policy terminated for reasons other than death the VA was to be queried periodically for advice as to whether the individual was still living.

The study has now been set to end with data for the year 1969. Thus, the follow-up period is 16 years, from 1-1-54 through 12-31-69.

Significance to Bio-Medical Research and the Program of the Institute:

This study continues to be one of the fundamental sources for information about smoking and health.

Major Findings: None this period.

Serial No. NHLI-BRB-6
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Proposed Course: The file has now been updated to include all known deaths from 1954 through 1969. The statistical analysis will be restricted to deaths from all causes. The proposed major analyses will take the form of life tables inwhich annual probabilities of dying (from all causes) are presented, as well as cumulative probabilities over the 16-year study period. Life tables will be specific for smoking, age and other categories. It is anticipated that the statistical analysis will be completed soon and a monograph prepared for publication.

Serial No. NHLI-BRB-7
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Framingham Study (This refers only to statistical services provided by the Biometrics Research Branch. The principal investigator for the study itself is Dr. William B. Kannel.)

Previous Serial Number: NHLI-BRB-10

Principal Investigators: Dewey Shurtleff, Tavia Gordon, Wayne Fercho, Frantz Ashley, Marthana Hjortland. (See above.)

Other Investigators: (See above.)

Cooperating Units: None

Man Years

Total:	6.5
Professional:	4.0
Other:	3.0

Project Description:

Objectives: To assist in data collection, tabulation and analysis for this long-term prospective study.

Methods and Findings: During the current year the data file for Exam 10 and the 18-year followup for changes in cardiovascular status have been completed and are now being used. Special files for menopause status, diabetes, lipoprotein analyses, etc. have also been prepared. Consultation has been provided on a continuing basis with respect to operation, analysis of data, preparation of talks and scientific reports, as well as on specific projects undertaken with outside collaborators.

Significance to Bio-Medical Research and the Program of the Institute: See Clinical Applications Section.

Proposed Course: See Clinical Applications Section.

Serial No. NHLI-BRB-8

1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Collaborative Studies (This refers only to statistical services provided by the Biometrics Research Branch. See general description in the Clinical Applications Section.)

Previous Serial Number: NHLI-BRB-11

Principal Investigators: Joyce Schiffman, Tavia Gordon

Cooperating Units: Collaborative Studies

Man Years:

Total:	1.5
Professional:	1.3
Other:	0.2

Project Description:

Objectives: To provide consultative services and statistical coordination and control to the collaborative studies which include the Framingham Study and the studies in Honolulu, Puerto Rico, Israel and Yugoslavia.

Methods: While each of the field epidemiological studies has its own objectives there is a need to compare results from the various studies. This requires work which is directed toward obtaining comparable data separate from that obtained as part of the individual studies. We have introduced inter-laboratory quality controls between Framingham, Hawaii and Puerto Rico. ECG's were exchanged among these three studies to establish a population at risk of developing myocardial infarction. The incidence of myocardial infarction in these studies is being determined by exchange of incidence ECG's and death certificates. This effort to attain comparability is providing a large diversified population in which to examine risk factors. Routine surveillance of response rates and follow up is undertaken. In addition we supply consultative and backup statistical services.

Significance to Bio-Medical Research and the Program of the Institute: See the Epidemiology Section.

Major Findings: See the Clinical Applications Section

Proposed Course: See the Clinical Applications Section.

Serial No. NHLI-BRB-9
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Coordinating Center Operations for the Urokinase-Streptokinase Pulmonary Embolism Trial

Previous Serial Number: NHLI-BRB-12

Principal Investigator: Christine Cole

Other Investigators: Thomas Hyers, James Neaton

Cooperating Units: NHLI Program Office and Medical Liaison: Blood Resource Program, NHLI; New York University Medical Center: Central Laboratory, 11 clinical investigators

Man Years:

Total:	2.50
Professional:	1.00
Other:	1.50

Project Description:

Objectives: To provide coordinating services required for the effective administration of a controlled cooperative clinical trial. The objective of the study is to compare the effects of three methods of therapy on the resolution rate of pulmonary thromboemboli: a 12-hour infusion of urokinase, a 24-hour infusion of urokinase, and a 24-hour infusion of streptokinase.

Methods Employed:

1. Consultation on study design.

2. Preparation of a protocol, manual of operations, and forms.

3. Preparation of randomization procedures; prevention of bias in treatment assignment.

4. Planning and developing systems for automatic data processing.

5. Data Processing.

6. Preparation of monthly progress reports for distribution to all study participants.

Serial No. NHLI-BRB-9
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

7. Preparation of periodic confidential reports containing data and analyses of results on complications of treatment, morbidity, mortality, and results of radiographic and hemodynamic studies. These reports are distributed to the Policy Board and the Advisory Committee for Statistical Analysis.

Major Findings: These will be made available at the completion of the study. There is a definite trend favoring one of the three treatment regimens appearing in the lung scan data; however, a similar trend is not evident in the analysis of angiograms.

Course of Project: This study is the second phase of the Urokinase Pulmonary Embolism Trial which was terminated in August of 1970. The present phase was started immediately after the conclusion of the first phase. Planning for the second phase began in the early part of 1970. The organizational structure and participating personnel are similar to those for the first phase. Eleven of the 14 clinical investigators from the first phase are participating in the second phase. As of May 15, 1972 a total of 133 patients had been accessioned into the study. Collection of data will continue at least through December 1972.

Serial No. NHLI-BRB-10
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: NHLI-VA Arthritis-Thromboembolism Study

Previous Serial Number: NHLI-BRB-13

Principal Investigators: Fred Ederer, Thomas Hyers, Louis Mesard, Lawrence Shaw, and James Neaton

Cooperating Units: NHLI Blood Resource Program and Veterans Administration

Man Years:

Total:	.20
Professional:	.20
Other:	-

Project Description:

Objectives: To determine whether an association exists between arthritis and thromboembolism. Recent laboratory work on the ability of aspirin to inhibit platelet aggregation suggests the hypothesis that aspirin can prevent the development of thromboembolism. Most rheumatoid arthritics take at least 6 tablets daily.

Methods Employed: The stated hypothesis will be tested in two interrelated studies, one a retrospective cohort study, the other a case-control study. The primary information source is the Veterans Administration Inpatient Discharge Data System (IDDS).

In the retrospective cohort study, the "incidence" of thromboembolism in arthritics and several non-arthritis control groups will be measured. Study patients will be selected from VA hospital discharges 1963-69, and their thromboembolism incidence, both venous and arterial, will be measured by the frequency of thromboembolism discharges from VA hospitals up to July 1, 1969. The names of study patients will also be matched against the VA "notice of death" file to determine vital status as of July 1, 1969. Death certificates will be obtained and analyzed by cause.

In the case-control study, thromboembolism and several groups of non-thromboembolism discharges during 1963-69 will be identified, and the frequency with which arthritis is recorded as an associated diagnosis will be used as a measure of arthritis prevalence.

Major Findings: None yet

Serial No. NHLI-BRB-10
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Course of Project: A detailed protocol for this study, including definitions of terms, classifications of diseases, case selection and exclusion criteria, control of co-variables, avoidance of bias, sample size considerations, methods of statistical analysis, etc., was finalized after a May 5, 1971 meeting with the advisory group. The Veterans Administration has prepared 19 data tapes of pertinent 1963-69 discharges from the IDDS and delivered them to the NHLI for case selection and data analysis. In addition, copies of the VA notice of death file for the years 1963-69 is being prepared and will be submitted to NHLI for analysis.

Significance to Biomedical Research: Some small-scale clinical trials of aspirin in the prevention of thromboembolism, both venous and arterial, have been conducted or are in progress now. The NHLI Committee on Thrombosis has discussed the possibility of large-scale field trials. Such trials require millions of dollars and many years to complete. While the possibilities of such trials are discussed, and tentative plans are formulated, the results of the present study could either weaken or strengthen the need for such field trials, or indicate, if aspirin is a potential prophylactic agent, whether it is more likely to prevent venous or arterial thromboemboli.

Serial No. NHLI-BRB-11
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Coordinating Center Operations for the Pilot Study for the Streptokinase-Urokinase Myocardial Infarction Trial

Previous Serial Number: NONE

Principal Investigator: Christine Cole

Other Investigator: C. Stephen Foster

Cooperating Units: NHLI Program Office and Medical Liaison: Blood Resource Program, NHLI; 8 clinical investigators

Man Years:

Total:	1.50
Professional:	.60
Other:	.90

Project Description:

Objectives: To provide coordinating services required for the effective administration of a controlled cooperative clinical trial. The objectives of the pilot study were to gain experience in patient recruitment and therapeutic management, to test protocol procedures and data forms, and in general to investigate the feasibility of a large scale definitive trial in Coronary Care Units to compare the effectiveness of thrombolytic agents with conventional care in reducing MI mortality.

Methods Employed:

1. Consultation on study design.
2. Preparation of a protocol, manual of operations, and data forms.
3. Preparation of randomization procedures; prevention of bias in treatment assignment.
4. Planning and developing systems for automatic data processing.
5. Data processing.
6. Preparation of monthly progress reports containing data on patient

screening and accession, information on problems encountered in implementing the protocol, schedules of meetings, etc.

Major Findings: None to date

Course of Project: This pilot study for the Streptokinase-Urokinase Pulmonary Embolism Trial was started in November of 1971 and is scheduled to continue until early fall of 1972 at which time it is anticipated that the definitive trial will begin. As of May 17, 1972 a total of 61 patients had been accessioned into the pilot study.

Serial No. NHLI-BRB-12
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: A study of cardiovascular mortality and weather in New York City for 1967

Previous Serial Number: None

Principal Investigator: Eugene Rogot

Other Investigator: Charles E. Sydenstricker

Man Years

Total:	1.5
Professional:	.3
Other:	1.2

Project Description:

Objectives: We plan to study the relation of a number of climatological factors to mortality from cardiovascular disease, respiratory disease and other diseases. In particular, we plan to examine the association between coronary deaths and snowfall.

Methods Employed: Reels of microfilm of death certificates for 1967 in New York City have been made available for use in the British-Norwegian migrant study. With the use of microfilm viewers, information is being coded for each death. There were a total of 87,606 deaths. The information collected will include place of death, (hospital or other) age at death, race, sex, month, day and hour of death, and the underlying cause of death. In addition, daily climatological data for New York City have been obtained for 1967 for maximum, minimum, and average temperature; total precipitation; snowfall and sleet; average and fastest wind speed; average barometric pressure, average dew point, relative humidity values and other variables.

Tabulations will be prepared to show variation of mortality from selected causes according to climatological variables, with deaths categorized by age, sex, and race. An attempt will be made to study the interrelations of variables by means of multivariate regression techniques.

Major Findings: None. Data processing has not been completed.

Serial No. NHLI-BRB-12
1. Biometrics Research Branch
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Significance to Bio-Medical Research and the Program of the Institutes:

A study of seasonal mortality patterns in New York city should be valuable in determining the generality of some of the new relationships brought out in the Chicago study. Further study of the association between coronary deaths and snowfall seems especially indicated.

Proposed Course: It is anticipated that the data processing and statistical analysis will be completed within the next year and the results prepared for publication.

ANNUAL REPORT OF THE HEART DISEASE EPIDEMIOLOGY STUDY

FRAMINGHAM, MASSACHUSETTS

July 1, 1971 - June 30, 1972

The Framingham Heart Disease Epidemiology Study has over the past year continued its curtailed NHLI function of maintaining a morbidity and mortality surveillance of cardiovascular disease through surveillance of hospital admissions and death certificates employing the core staff of 5 persons. This has been rendered more comprehensive by the implementation of the B. U. M. C. periodic re-examinations under private funding. We are thus able to continue to obtain an undistorted picture of the evolution of cardiovascular disease including those cases unrecognized or too mild to seek medical attention or those treated without hospitalization.

With the high rate of additional cases accumulating at an accelerated rate in this aging population it is now possible to examine prospectively the relation of factors introduced late in the study to the rate of subsequent development of cardiovascular disease. Thus, plans are being made to analyze the relation of diet, emotional stress, thyroid function, impaired glucose tolerance, corneal arcus, presbyopia, physical activity, coffee habit, among others to the rate of development of cardiovascular disease including CHD, CVA, I. C. and CHF.

The additional follow-up is allowing a more precise delineation of the natural history of established cardiovascular disease. Thus, we are able to begin analysis of the rate of infarction, sudden death, congestive failure, strokes and survival in subjects who developed angina pectoris or myocardial infarction under observation. Such information is sorely needed to help evaluate the efficacy of surgical intervention for ischemic heart disease. While it is no substitute for a controlled clinical trial it may provide some standard of comparison. Such information is eagerly sought after by those attempting to define the indications for revascularization of the myocardium. After some time we may even be able to identify those factors which affect prognosis. We shall attempt to develop a prognostic index identifying coronary victims likely to do badly for vigorous prophylactic intervention.

Research projects being actively pursued by the NHLI staff include: the role of hypertension in the development of congestive failure; the use of the vital capacity to predict congestive failure; development of a coronary profile hand book; clinical characteristics of the unrecognized myocar dial infarction; the prevalence of abnormal lipoprotein types; the natural history of myocardial infarction; factors related to suddenness of coronary death; the relation of left anterior hemiblock to CHD; the role of obesity in sudden death; the sensitivity and specificity of peripheral pulse wave recordings in detecting intermittent claudication; the ECG precursors of sudden death; the relation of finger pulse recordings to the development of C-V disease; the usefulness of systolic time intervals in prediction of congestive failure and the evolution of intraventricular conduction disturbances among others. Factors related to development of CHD in women, particularly premature

menopause, are being explored.

In addition to the foregoing, the core staff is involved in conducting a study of the offspring cohort to elucidate the role of familial factors in the occurrence of hyperlipoproteinemia. In addition assessment of ECG, blood pressure, degree of adiposity, and cardiovascular disease status is being made to determine if these too cluster in families. In order to complete this on an extended sample the contract with the Framingham Union Hospital to provide the required laboratory, ECG and secretarial services will be extended for an additional year. The clinic facilities for this endeavor is, however, in jeopardy since the hospital expansion program will probably require that they confiscate this space. New clinic facilities will have to be found.

Thus far the study appears to be progressing well and 1153 offspring have been examined and lipoprotein typing accomplished.

The B. U. M. C. recycling of the original Framingham cohort has gotten under way and re-examinations are proceding on schedule so that the entire cohort will be processed within 2 years. The NHLI core staff is collaborating in the conduct of these examinations and supervising the collection and processing of the data. This endeavor is funded from private sources through the efforts of Dr. T. R. Dawber and the B. U. M. C. fund raising staff. High quality clinical appraisals are being obtained up to the usual standards of the Framingham Study. New innovations include systolic time interval measurement to assess left ventricular function and pulse wave recordings to assess peripheral arterial patency. The interface between B. U. M. C. and NHLI staff at Framingham is tranquil and an efficient integration of activities without duplication of effort has been achieved.

The B. U. M. C. - N. I. N. D. stroke surveillance grant has been implemented and is proceeding well. New cases which have evolved have been evaluated by qualified neurologists while hospitalized, on return to the clinic for periodic re-examination and a special neurology clinic set up to clarify all suspect cases uncovered during the regular clinic examinations. This is proceeding extremely well, providing well-documented cases of each particular variety of stroke for epidemiologic study.

Collaborative Studies

A collaborative study of the efficacy of systolic time intervals in predicting congestive heart failure has been implemented under the supervision of Dr. David Spodick. Thus far close to 1000 subjects have been evaluated. A preliminary analysis of a case-matched control group is being completed to ascertain whether the procedure can discriminate persons with an etiology for impaired left ventricular function, but as yet no overt evidence

of congestive failure.

A study of the disability of stroke victims has been implemented under the supervision of Dr. Gresham of Tufts. A specially trained nurse is making the assessments using a structured form by visiting the subjects in their homes or in nursing homes. The epidemiology of stroke in the Framingham Study population is further described. The functional, social and vocational status of persons who have survived completed stroke are assessed at least six months after onset of the stroke by the Nurse-Investigator supported by the RT-7 grant at Tufts University School of Medicine. These assessments permit a correlation of functional, social and vocational outcome as well as survival with the various types of stroke. With appropriate analyses, it will be possible to look at the relationship between precise location of the lesion in completed stroke, the comorbid processes, and relate these to social, vocational, other host characteristics and functional factors as well as to survival.

Of the 100 surviving persons who have had a completed stroke to date in the Framingham population, thus far 25 persons have had a functional, social and vocational assessment. (14 women and 11 men).

The first phase of the Framingham-Albany collaboration on the study of Sudden Death has been completed. Precursors of sudden death incidence have been analyzed, presented at medical meetings, revised and is now being readied for publication. The next phase concerned with factors related to suddenness of coronary fatality (i.e., particularly related to sudden death) is underway. The final phase will involve a detailed examination of the ECG precursors of sudden death.

Collaborative studies of autopsy findings in the Framingham cohort in relation to antecedent premorbid attributes are being carried out in cooperation with Dr. Gherardi of the Framingham Union Hospital pathology department, and supported by B. U. M. C. A protocol is being developed which includes detailed dissection, quantitative assessment of coronary involvement, and myocardial pathology using special stains and postmortem angiography. More extensive neuropathologic examinations of brains have been instituted in collaboration with B. U. M. C. All these activities are funded through B. U. M. C. under the auspices of Dr. T. R. Dawber.

The lipoprotein phenotyping project has been completed and the Framingham cohort has been typed. However, in view of the continued operation of the laboratory for the offspring study an effort is being made to obtain typing on those in the cohort who missed an examination, were nonfasting, or were unsatisfactorily typed in order to obtain as complete a prevalence estimate as possible. This has provided the propositi for studies of offspring for familial aggregation of lipoprotein types and will

form the basis for a prospective analysis of the relation of lipoprotein types, as currently defined, to the subsequent development of atherosclerotic diseases to be ascertained from continued cardiovascular surveillance. Analysis of the lipoprotein data has not been completed but already suggests that less than a fourth of established coronary cases fall within the "typable" category of lipoprotein abnormality.

The laboratory functions have been conducted by the lipid laboratory of the Framingham Union Hospital under the direct supervision of Dr. William Castelli. Currently the laboratory has been doing a complete lipid profile on all offspring who return to the clinic fasting. This profile includes eight separate operations: Total cholesterol, alpha cholesterol, bottom fraction cholesterol, triglyceride, a preparative spin in the ultracentrifuge and three lipoprotein electrophoretic strips on paper.

The information acquired will help to determine whether the lipoprotein type determined on the offsprings parent will qualify for a familial designation or not. These typings on the offspring will also be analyzed to determine the familial aggregation of types or components of the lipid profile To date 1264 typings have been done in the laboratory and it is calculated that 1450 will be completed by June 30, 1972.

The current personnel in the laboratory comprise a supervision consultant, one full-time laboratory technician, two part-time laboratory technicians and a dish washer.

Eye Institute Contract

The Eye Institute is negotiating a contract with the B. U. M. C. group to conduct studies of cataracts, glaucoma and blindness in the Framingham cohort. The occurrence of these will be examined in relation to antecedent personal attributes and living habits already measured in the Framingham cohort.

Cancer Institute Contract

The NCI has contracted with B. U. M. C. to have Framingham cohort records reviewed for the occurrences of cancer diagnoses. All the records of the 1070 deaths in Framingham have thus far been reviewed revealing 335 persons with cancer: 61 colon and rectum, 43 breast, 36 lung, 25 stomach, 22 gynecological plus 148 at various other sites. When the charts of the remaining living subjects are completed the NCI staff will verify the diagnoses according to specified criteria. It will then be possible to study the precursors of specific cancers in the cohort both from the standpoint of personal attributes and living habits but also from the characteristics of their frozen sera collected biennially over the years both prior to or following

the appearance of malignancies.

Publications over the past fiscal year numbered 31. Some were requested by the publishers as parts of seminars and book chapters, others were originated by the Framingham staff. There has been no evidence of a waning productivity despite curtailment of direct NHLI involvement in Framingham. The NHLI biometric support has been most helpful in attaining the quantity and maintaining the quality of the Framingham research output. Here appended is a list of publications for the fiscal year 1971.

1. Relative importance of factors of risk in the pathogenesis of coronary heart disease. The Framingham Study. Kannel, W.B., Castelli, W.P., Verter, J., McNamara, P.M.: In Russek, H.I., Zohman, B.L. (Eds.) Coronary Heart Disease. A Medical - Surgical Symposium sponsored by the American College of Cardiology and St. Barnabas Hospital, New York City. Dec. 13-15, 1968. Philadelphia, J.B. lippincott, pp. 97-114, 1971.

2. Current status of the epidemiology of brain infarction associated with occlusive arterial disease. Kannel, W.B.: Stroke, 2:295-317, July-Aug. 1971.

3. Lipid profile and the potential coronary victim. Kannel, W.B.: Amer. J. Clin. Nutr. 24:1074-1081, Sept. 1971.

4. Physical activity and coronary vulnerability. The Framingham Study. Kannel, W.B., Gordon, T., Sorlie, P., McNamara, P.M.: Cardiol. Digest. 6:28-40, June 1971.

5. The disease of living. Kannel, W.B.: Nutrition Today, 2-11, 1971.

6. The coronary-prone patient. Roundtable discussion based on a patient care discussion - consultants - Amsterdam, E.A., Callard, G.M., Hellerstein, H.K., Kannel, W.B., Ostrander, L.D., Wanger, N.K., representing Patient Care: Bulger, J.J., Felder, E.A.: Patient Care, 18-52, Aug. 1971.

7. Serum cholesterol, lipoproteins and risk of coronary heart disease. Kannel, W.B., Castelli, W.P., Gordon, T., McNamara, P.M.: Abstract from Ann. Intern. Med. 74:1-12, 1971. In Cardiology Digest, July, 1971. p.19.

8. Sudden death from coronary heart disease. Gordon, T., Kannel, W.B.: Abstract from JAMA 215:1617-1625, 197p. In Modern Medicine, Sept. 1971, 1:119.

9. Risk factors in stroke due to cerebral infarction. A statement for physicians prepared by a subcommittee and approved by the executive committee of the council on cerebrovascular disease of the American Heart Association. Kannel, W. B., Chairman. Vol. 2, Stroke, Sept-Oct. 1971, pp. 423-428.

10. The relation of physical activity to risk of coronary heart disease. The Framingham Study. Kannel, W. B., Sorlie, P., McNamara, P.M.: In Larsen, O. A., and Malmborg, R. O. (Eds.) Coronary Heart Disease and Physical Fitness. Proceedings of a Symposium held in Copenhagen, Sept. 2-5, 1970. Baltimore University Park Press, 1971, pp. 256-270.

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19. Systolic pressure and heart disease risk. (Abstract) Kannel, W. B., Gordon, T., Schwartz, M. J.: Modern Medicine, Dec. 1971.

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29. Role of blood pressure in the development of congestive heart failure. The Framingham Study. Kannel, W.B., Castelli, W.P., McNamara, P.M., McKee, P.A., Feinleib, M.: In press.

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Highlights of Framingham Research

As indicated in the foregoing publications a number of research areas have been covered, some new and others further evaluation of previously covered topics.

Relative Importance of Factors of Risk in the Pathogenesis of Coronary Heart Disease:

The natural history of coronary heart disease (CHD) may be discerned with a minimum of distortion from an investigation of the way in which it evolves and terminates fatally in a general population sample. Because asymptomatic as well as symptomatic cases, cases not hospitalized as well as those reaching medical care and cases dying too suddenly to reach the hospital are included, a more comprehensive picture of its entire spectrum is realized.

Current Status of the Epidemiology of Brain Infarction Associated with Occlusive Arterial Disease:

Although large gaps in our knowledge concerning the epidemiology of cerebrovascular disease are apparent, careful inspection of all existing data now makes it possible to see certain patterns emerging which suggest certain risk factors for stroke.

While the problem of differential diagnosis of the various categories of cerebrovascular disease presents a major obstacle to obtaining an undistorted picture of the epidemiological features of stroke from death certificate mortality data, the addition of evidence from prospective studies, including those in Framingham, Massachusetts, reveals that various types of arterial occlusion with cerebral infarction are by far the most prevalent type of stroke. Any specific origin of atherosclerosis remains obscure, as possible etiological candidates including dietary alterations in salt, fat and refined carbohydrate, sedentary living, excessive calories promoting obesity, the cigarette habit and even the mineral content of water in addition to marital status have all been incriminated. However uncertain the final answer is, certain precursors for atherosclerosis, such as hypertension, diabetes, and hyperlipidemia, are important. Of these, hypertension is clearly the most important contributor to stroke incidence. Certain combinations of items carry more risk than do the same items singly. For example, the risk of a brain infarction in diabetics with hypertension is probably about six times that of normal subjects. In persons under 50 at the time of measurement risk of cerebral infarction is possibly ten times higher in those with hypertension and elevated lipids than in those without either elevated. This compounding of risk has pathogenetic, preventive and public health implications.

For purposes of stroke screening alone the most efficient and practical method would be to determine casual blood pressure.

Lipid Profile and the Potential Coronary Victim:

A considerable body of evidence has accumulated which links the total blood cholesterol with the development of atherosclerosis and its principal lethal manifestation, coronary heart disease (CHD). This has incited much research concerning the role of lipids in atherogenesis and, as a result, virtually every blood lipid fraction has been incriminated (1). Nevertheless, the lipid component most basic to the atherosclerotic process remains uncertain. Those lipid elements incriminated include cholesterol, triglyceride, phospholipid, and non-esterified fatty acids. In addition, the lipoproteins and proteins to which the lipids are linked for transport have also been blamed. These include the cholesterol-rich beta lipoproteins of the S_f0-20 class, the triglyceride-rich pre-beta lipoproteins of the S_f20-400 class, the alpha lipoprotein rich in phospholipid and the albumin fraction, which carries the fatty acids about. Whether one or several of these are fundamentally involved in atherogenesis is not clear. Furthermore, all the lipoprotein fractions transport some cholesterol and it is not clear whether the partition of the total cholesterol among these fractions influences its atherogenicity. Also, serum cholesterol values can reach a high value through a number of mechanisms. It may be secondary to other diseases that affect lipid metabolism in different ways (i. e., diabetes, thyroid disease, obstructive liver disease). It may be "primary" and caused by some ill-defined disorder of lipid metabolism resulting from an "abnormal" diet or faulty handling of a "normal" diet. Sometimes it is caused by excess alcohol consumption. It may also be the result of inborn errors of lipid metabolism. The atherogenicity of each variety of hyperlipidemia requires further clarification. The Framingham Study is attempting to resolve some of these questions.

Physical Activity and Coronary Vulnerability:

There is an increasing concern as to whether man in his transformation by technologic "progress" from a physically active to a sedentary creature has incurred an increased vulnerability to lethal cardiovascular disease. Evidence that this may well be true is accumulating from studies of both the general population and a variety of occupational groups. Some prospective epidemiologic investigations of living habits in relation to cardiovascular disease have shown a lack of exercise to be a prominent feature in the background of the coronary victim. The present report deals with this issue once again, reflecting on the pertinent findings from the Framingham Study. It explores the relationship of reported physical activity status to development of fatal and nonfatal coronary heart disease (CHD). A distinct relationship was found and by multivariate analysis it was shown

that neither associated hypertension, hypercholesterolemia nor obesity can explain the association of sedentary levels of physical activity with increased vulnerability.

Risk Factors in Stroke Due to Cerebral Infarction:
Quote from the Editor of Stroke (Clark Millikan): "In 1968 the Council on Cerebrovascular Disease of the American Heart Association authorized the appointment of a subcommittee to produce a statement concerning "Risk Factors for Stroke." After working for over a year the subcommittee reported that, because of inadequate data concerning " all or several of the factors," they had been unable to produce a statement satisfactory to each subcommittee member. Some were reluctant to set down a policy statement until every loophole was plugged - a task made extraordinarily difficult by the complexity of Stroke and the fact that prospective studies of large population groups are necessary for the acquisition of some needed data. Another problem was that of interpreting the phrase risk factors. Does this phrase imply that eliminating or minimizing a "risk factor" (for example, maintaining successful control of hypertension) automatically reduce the risk of Stroke for that individual? This therapeutic consideration may await an answer for years, although it must be admitted that the term "risk factors for Stroke" does suggest that careful treatment of one or several risk factors can help to prevent Stroke. In any event, the subcommittee was admonished by its chairman, Dr. William Kannel, to consider the task a never-ending one; that data are now available indicating that certain phenomena are more commonly followed by Stroke and that these phenomena (culprits) should be publicly identified as elements or risk factors for Stroke. The subcommittee decided to work first with the profile of the candidate at risk of a cerebral infarction - and so state. The subcommittee realistically writes: "Any statement arrived at will be subject to periodic revision as more information is accumulated!" Obviously, new data may make changes necessary! Under Dr. Kannel's talented and dedicated leadership the subcommittee produced the statement which appears in the Journal "Stroke".

The Natural History of Congestive Heart Failure:

The natural history of congestive heart failure was studied over a 16-year period in 5,192 persons initially free of the disease. Over this period, overt evidence of congestive heart failure developed in 142 persons. In almost every five-year age group, from 40 to 62 years, the incidence rate was greater for men than for women. Although the usual etiologic precursors were found, the dominant one was clearly hypertension, which preceded failure in 75 percent of the cases. Coronary heart disease was noted at an earlier examination in 39 percent, but in 29 percent of the cases it was accompanied by hypertension. Precursive rheumatic heart disease, noted in 21 percent of cases of congestive heart failure, was accompanied by hypertension in 11 percent. Despite modern management, congestive

heart failure proved to be extremely lethal. The probability of dying within five years from onset of congestive heart failure was 62 percent for men and 42 percent for women. This report which appeared in the New England Journal of Medicine precipitated two editorials and three letters to the editor.

Habits and Heart Disease:

There is mounting evidence to suggest that man, by altering his environment, has promoted an increasing incidence of coronary heart disease. The replacement of muscle power with machines, enrichment of the diet with hard fat, cholesterol and calories, and manufacture and promotion of the ready made cigarette appears to have exacted a toll in increased mortality from cardiovascular disease. Possibly as a result, the cardiovascular sequelae are now the chief force of mortality in affluent nations. About half of all deaths in the U. S. are from cardiovascular causes and coronary disease; a cerebrovascular accident, and congestive failure is all too frequently the reward for achieving an advanced age. Most of these deaths arise from atherosclerotic or hypertensive disease. The dominance of cardiovascular diseases as a force of mortality is largely a tribute to the revolution in our understanding of the epidemiology and consequent control of infectious and nutritional deficiency diseases. This has produced a radical alteration in the pattern of disease and forces of mortality acting on the population. Mortality early in life dropped sharply and as more people survived to older ages they have become increasingly subject to the influence of the chronic and "degenerative" diseases. Thus, the chronic cardiovascular diseases, like some bedrock of mortality have emerged as the layers of infectious and nutritional disease was removed.

The results of this study have demonstrated that certain living habits are associated with excess risk of developing coronary heart disease. The findings provide clues to possible causes of coronary heart disease and suggest means of prevention, since habits and environment are susceptible to change. For example, excessive cigarette smoking, obesity, and sedentary living are among suspect factors associated with increasing the chances of developing coronary heart disease. It is worthwhile, therefore, to direct attention to the findings concerning such habits and the potentials for health improvement that may lie in their alteration.

Natural History of Angina Pectoris in the Framingham Study:

The evolution of 303 cases of angina in a general population sample of 5,127 persons was ascertained and revealed that the lot of the angina victim is not a happy one. Prognosis as to survival and progression to more serious coronary manifestations was discouraging in men. One in four men with angina can expect to have a coronary attack within five years.

The risk is half this for women. About 30 percent of those over 55 will die within eight years, and 44 percent of the coronary deaths will be sudden. Mortality was close to that which follows the posthospital phase of myocardial infarction. Surprisingly survival in men with uncomplicated angina was no better than that for angina which follows an infarction.

Angina was more likely to be the presenting complaint of coronary disease in women (65 percent) than in men (37 percent). In men 45 percent of angina arose out of myocardial infarction compared to 15 percent in women. Half of those sustaining initial myocardial infarctions had angina following it, 31 percent experiencing it for the first time. In those with angina who sustained an infarction, the angina disappeared in only 15 percent of men and no women, a rate lower than the 30 percent spontaneous rate of disappearance. Only 23 percent of infarctions were preceded by angina. Almost one in four myocardial infarctions were silent or went unrecognized. Such infarctions were rare in persons with prior angina.

The Framingham Study of Coronary Disease in Women:

Male chauvinists that we are (or at least are accused of being), we have too long concentrated our study of the evolution of coronary heart disease on male subjects. This is, and has been, unjustified on two counts: First, because explanation for the relative immunity of the premenopausal women has implications for retarding the disease in the male. Second, because the disease, while far less common in the female, nevertheless kills more women than any other single cause. The role of lipids in development of CHD in women is reported and differences in the contribution of cholesterol and endogenous triglyceride in older men and women pointed out.

Atherosclerosis as a Pediatric Problem:

Atherosclerosis, most frequently manifested as coronary heart disease, is the major health concern in the United States. This disease of adulthood has its origins in infancy and childhood. Genetically determined lipid abnormalities account for a distinct but small segment of highly susceptible persons. Early detection of such individuals and correction of their lipid defects would appear to be indicated in an effort to delay the atherosclerotic process. Other more common traits also having origins early in life are hypertension, acquired lipid defects, diabetes mellitus, obesity, the smoking habit, and a sedentary way of life. Attention by the pediatrician to the prevention and early treatment of these "defects" is urged.

The Natural History of Arteriosclerosis Obliterans:

Information concerning the prognosis in patients with occlusive

disease of the peripheral arteries is quite scarce, and that which assess the impact of such disease independent of associated cardiovascular impairments is virtually non-existent. Although extensive observations have been made concerning the ways in which persons with intermittent claudication (I. C.) or peripheral occlusive arterial disease differ from "normal", very little prospective information is available concerning the precursors of I. C. and the magnitude of the risk associated with them. Also, little is known concerning the manner in which this disease arises, evolves, and terminates fatally in the general population. Most previous studies of the natural history of peripheral occlusive arterial disease, and I. C. in particular, have been handicapped by an inability to obtain samples of patients which are representative of the total disease experience.

The Framingham Study was in a position to overcome some of these difficulties by following a large representative sample of the general population and subjecting them to routine periodic medical evaluation documenting all evidence of peripheral occlusive arterial disease obtainable from a comprehensive medical surveillance of the population including, in addition to biennial cardiovascular examination, review of hospital and physicians' records, medical examiners' reports, and death certificates. This report examines in a general population the manner in which I. C. arises, evolves and becomes complicated by more serious cardiovascular impairments, and terminates fatally. The findings suggest that it is feasible to identify persons who are vulnerable to occlusive peripheral arterial disease. The ingredients of this profile are similar to those which predict CHD. More than half of I. C. subjects had pre-existing or co-existing potentially lethal overt C-V disease. The I. C. itself proved a rather benign disease and the principle justification for detecting it early is to identify persons who require careful C-V evaluation.

STAFF: FISCAL YEAR

N. H. L. I., Morbidity and Mortality Surveillance: Offspring Study:

William B. Kannel, Medical Director
William P. Castelli, Senior Surgeon
Marguerite D. Beattie, Secretary (GS-6)
Patricia M. McNamara, Statistician (GS-12)
Ruth C. Anderson, Statistical clerk (GS-5

Lipoprotein Contract

Doris E. Honey, Receptionist (GS-4)
Carleen C. Simoneau, R. N. (GS-6) Temp. part-time.
Karen A. Pierozzi, (GS-4) Temp.

Consultant
Thomas R. Dawber, Cardiologist

Status of Follow-up

The 18 year follow-up has been completed and the following disease endpoints entered into the tape: 674 cases of CHD, 192 cases of CHF, 193 cases of CVA (108 of ABI), 253 cases of I. C., and 1001 deaths. All have been verified and reviewed to determine if they meet specified criteria. This represents a net gain of 235 cardiovascular events in the two years since the 16 year follow-up. About a third of these cases would have been missed were it not for the re-examination of these subjects in the clinic. A 20 year follow-up will be available in September 1973. (Table 1).

At this time it is not possible to estimate what the loss to follow-up has been. The B. U. M. C. is planning to assess this at the midpoint of the re-examination cycle in September 1972.

Five Year Plan for Framingham:

Over the next five years major emphasis should be placed on data analysis rather than further data collection. Continued surveillance of the population for mortality and cardiovascular endpoints of myocardial infarction, congestive failure and cerebrovascular disease based on hospital admissions is warranted in any event. Additional information from the B. U. M. C. recycling of the cohort will provide non-hospitalized interim cardiovascular events such as CHF, I. C., A. P. and unrecognized M. I. The latter would, of course, be grossly underestimated by reliance entirely on hospital and death certificate data. B. U. M. C. recycling should be encouraged and supported as long as the follow-up continues reasonably complete.

One of the unique features of the Framingham Study is that it contains data on women. Major emphasis should be placed on examination of the precursors of C-V mortality and morbidity in women. Now that incidence is reaching sizeable proportions detailed analysis should be undertaken. In addition to the standard risk parameters those particularly related to the female sex need scrutiny: - parity; premature surgical menopause; age at natural menopause; hormone therapy, etc.

With the current interest in surgical intervention for established coronary heart disease it is becoming increasingly important to have some solid data on its natural history. While not as satisfactory as a controlled clinical trial this will provide some standard of comparison for these surgical interventions. We therefore should try and aquire undistorted information on the MI rates, survival, sudden death and CHF rates of angina and MI patients. Since this would include all subjects with the disease and not only those under medical care it can provide a more comprehensive appraisal of the prognosis of established CHD. In addition, we should attempt to develop predictive profiles which will distinguish those with established CHD likely to have recurrences, sudden deaths and a truncated survival from those who

Table 1
Cardiovascular Disease Outcomes Available for Analysis

		18-Year Follow-up	Reviewed in Interim	5/30/72 Total
CHD				
	Men	422	86	508
	Women	252	66	318
		674	152	826
CHF				
	Men	104	39	143
	Women	88	26	114
		192	65	258
CVA				
	Men	95	23	118
	Women	98	27	125
		193	50	243
ABI				
	Men	50	16	66
	Women	58	15	73
		108	31	139
I. C.				
	Men	98	16	114
	Women	155	13	168
		253	29	282
Deaths (5-5-71)				
	Men	571	40	611
	Women	430	30	460
		1001	70	1071

have a reasonably normal life expectancy. There is every reason to believe that this can be done with reasonable precision.

Studies of non-invasive appraisal of cardiac function, peripheral circulation and extracranial vascular disease should be continued and new ones promoted. These can be tested for efficacy in predicting C-V events such as CHF, CVA's and I. C. within a short period in this aging population. These can be accomplished under contract with B. U. M. C.

The focus of major emphasis should be shifted from CHD to CVA, CHF and OPAD for the major risk factor analysis. There is still a paucity of prospective information concerning the precursors of these C-V end-points. Sudden death should also be studied in more detail as numbers accumulate.

More studies of the determinants of the high prevalence of hyper-lipidemia, hypertension and impaired glucose tolerance should be initiated using the maximum follow-up (i. e., 18-20 years), including spouse aggregation; familial clustering in sibs and offspring; relation to energy balance and other personal attributes.

Analysis of the relation of later introduced variables to C-V disease outcomes should be undertaken as the follow-up disease incidence becomes adequate.

The feasibility of further assessment of pulmonary function should be examined. Those who, on previous examinations are identified as having obstructive disease (from flow rates, FEV; etc.), should be studied in detail to verify the diagnosis according to some firm criteria and the severity of the impairment quantitated. This will establish the incidence in a general population sample and its relation to environmental factors such as cigarettes and occupation, and also, familial aggregation can be studied.

Studies of offspring for aggregation of lipoprotein types, blood pressure, weight pattern, glucose tolerance and pulmonary flow rates, will be completed in one more year. It is possible that an additional year to obtain as many offspring of the families selected as possible to reduce the number of unknown family members to a minimum may be justified.

Resources to achieve these goals consist of those currently in hand, plus one additional medical officer - investigator, to assist with the procedures required. Additional space will be required for any new procedures added. Contract arrangements will be required to obtain pulmonary function function evaluation. Other goals will depend upon developing a congenial, effective collaborative working relationship with the B. U. M. C. group conducting the re-evaluation of the Framingham cohort. This will depend upon

ensuring ready access to the past data and sharing custodianship of the population with them.

In so far as the NHLI has been disinclined to continue periodic re-examinations of the original Framingham cohort, the possibility for implementing new procedures in it directly, is nil. This can be accomplished through B. U. M. C. or the NHLI can reconsider its position and reinstitute periodic examinations in the cohort for so long as the follow-up remains reasonably complete.

A collaborative study of cancer morbidity and mortality is being carried out with a view to examining frozen sera before and after development of cancer controlled by the cohort sera for the same time intervals. We are participating in an interstudy comparison of CHD incidence in Hawaii, Puerto Rico and Framingham to see if incidence and prevalence varies in those areas and to what extent differences in known risk factors explain these differences, and which factors are most responsible for the differences.

PHS-NIH
NATIONAL HEART AND LUNG INSTITUTE
July 1, 1971 through June 30, 1972

FIELD EPIDEMIOLOGY RESEARCH SECTION

The Field Epidemiology Research Section is engaged in a variety of studies dealing with the epidemiology of cardiovascular disease. These include studies of genetic influences and familial aggregation of coronary risk factors, analyses of the natural history of cardiovascular disease, and surveys of the incidence and circumstances surrounding the occurrence of acute cardiovascular events.

The NHLI Twin Study was extended to two new areas during fiscal year 1972. Continuing the contracts to the Mt. Zion Hospital with Dr. Ray Rosenman as principal investigator and to the University of California at Davis with Dr. Nemat O. Borhani as principal investigator, a subcontract was let to the Rancho Los Amigos Hospital with Drs. Ronald Selvester and John Wagner as co-principal investigators to extend the NHLI Twin Study to include approximately 150 sets of twins residing in Southern California. The core protocol will be identical to that used among the Northern California twins examined at Mt. Zion Hospital and Sacramento Hospital Center but will also include detailed studies of vectorcardiographic characteristics of the twins. Under a contract to Indiana University with Dr. Joe C. Christian as principal investigator, approximately 70 sets of twins residing in the Indiana area have been examined according to the core protocol. It is hoped that eventually 170 sets of twins residing in Indiana will be incorporated into the collaborative twin studies. Analysis of the data gathered on the twins residing in Washington, New England and Northern California has been proceeding, and a joint meeting of investigators was held in Tampa, Florida, in February, 1972, to discuss further analyses and publication plans. It is hoped that a monograph covering the analyses of the twin data will be prepared in fiscal year 1973. Miss Marthana Hjortland has examined the dietary histories of the twins in New England and Washington, and used the resulting analyses for her doctoral thesis from the University of Minnesota.

A significant new project initiated in fiscal year 1972 is a joint effort of the Field Epidemiology Research Section and the Framingham Heart Program to study the offspring of the 1644 spouse sets that were part of the original Framingham cohort. This Framingham Offspring Study will explore the various familial and genetic associations in parents and their offspring in regard to cardiovascular risk factors, primarily those relating to the lipid fractions, and will attempt to obtain baseline data on cardiovascular prevalence and incidence for exploring secular trends in the disease in the two generations. The Framingham Heart Study staff has assembled a roster of all offspring of these spouse pairs and telephone contact has been made with many of them to invite them in for examinations at the Framingham facilities. The response to date has been excellent, especially among those whose parents have continued to participate in the original Framingham Heart Study. Approximately 1200 offspring have been examined in fiscal 1972 and it is hoped that in perhaps another 18 months upwards of 4000 of the offspring will be examined.

The Framingham Cardiovascular Disease Survey which was launched in June of 1970 has completed the collection of data on all patients hospitalized in the town of Framingham through June, 1971. During the current fiscal year an intensive search of all admissions to all other hospitals in the state of Massachusetts and to nursing homes in the Framingham area has been conducted in order to identify cardiovascular events which may have occurred among Framingham residents but which were treated in facilities outside of the town of Framingham. This effort was greatly facilitated by the availability of computerized records in many of the hospitals but a great deal of effort in the form of hand searches of admission records has been required to ensure completeness. All the cases are undergoing clinical review in a manner uniform to that used in the Framingham Heart Program to enable comparable analyses of the incidence in the survey year as compared to the 20 years of experience of the Framingham cohort. Among the 65,000 residents living in the town of Framingham on April 15, 1970, according to the U.S. Census, over 700 cardiovascular events occurred between June, 1970, and June, 1971. Although analyses are not yet complete preliminary results indicate that "hard endpoints" had similar incidence in both the survey and the Framingham longitudinal study.

A collaborative arrangement for the analysis of data obtained from the study of 345 acute coronary events which occurred in Montgomery County, Maryland, during 1969 has been continuing. This study attempted to delineate the pattern of action taken by individuals who availed themselves of medical care and to contrast these actions with those of people who did not avail themselves of medical facilities and who consequently died outside of hospital. An effort has been made to quantitate the components of delay in reaching medical facilities as well as the type of action engaged in by patients in order to diagnose and alleviate their acute symptoms. It has not been possible to relate long delay or types of response to demographic characteristics of the patients, but rather to the "emergent" aspects of the acute coronary event, i.e., the intensity and nature of the symptoms tend to govern the patient's response and actions rather than any stereotyped behavior patterns which may be characteristic of a group. In conjunction with these analyses a mortality study of the corresponding 25 census tracts in Montgomery County was undertaken to get a clearer picture of the overall impact of out of hospital cardiovascular mortality. It was clearly documented that over 60 percent of cardiovascular fatal events occurred outside of hospital. Although there is a median delay of several hours for those who do make it to hospital, the primary component of this delay is the patient's indecision about the true significance of his early symptoms rather than delays in obtaining transportation to medical facilities.

Analyses of the Framingham material have continued. Of particular interest have been the studies relating to the aggregation of cardiovascular risk factors among first degree relatives and spouses who participated in the original Framingham study. Significant correlations for the cardiovascular risk factors of blood pressure, Framingham relative weight, cholesterol level and cigarette smoking were found among 600 sibling sets available for analyses.

The degree of association remained stable for the 18 years of data available although the sibs may be presumed to have been living apart during this period. It thus appears that the degree of familial aggregation for risk factors observed in middle-aged persons is conditioned by environmental factors which operated early in life and/or by truly genetic factors. Other aspects of these relationships will hopefully be elucidated by continued observation of the cohort and analyses of the data to be obtained on the offspring of these individuals.

The staff of the Field Epidemiology Research Section is also engaged in several literature reviews to document significant new areas for development in the next few years. The role of carbon disulfide in increasing cardiovascular mortality among viscose rayon workers has been reviewed in an article in the American Heart Journal and several contacts have been made to try to investigate this problem in American industrial groups. Reviews are continuing of other industrial hazards and exposures in relation to cardiovascular mortality, of the role of hard water and trace metals in leading to atherosclerosis, and of the role of psychosocial stress in promoting cardiovascular morbidity. Dr. Robert Brasch completed a review of the extramural grants program as it relates to studies with primary interest in epidemiological problems. This will serve as a useful background for planning future program activities and research areas.

Serial No. NHLI-FERS-1
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: A Twin Study of Genetic Factors in Cardiovascular Diseases

Previous Serial Number : NHLI-FERS-1

Principal Investigator: Manning Feinleib, M.D.

Other Investigators: Robert J. Garrison, M.S.
Nemat O. Borhani, M.D.
Ray Rosenman, M.D.
J. Theodore Schwartz, M.D.
Jeanne Tillotson, M.A.
Marthana Hjortland, M.P.H.

Cooperating Units: Section on Ophthalmic Field and Developmental Research, NEI
Framingham Heart Study

Man Years (NHLI only)

Total:	2.0
Professional:	1.6
Other:	0.4

Project Description:

Objective: To evaluate the relative contribution of environmental and genetic factors to the development of cardiovascular diseases (CVD) and to the levels of risk factors associated with CVD.

Methods Employed: 400 pairs of male twins aged 42-55 have been examined according to a standard protocol in 6 areas of the United States. Data have been gathered about past environmental, family, and medical history and measurements of physiological variables including lipoprotein determinations have been obtained. The data will be analyzed by correlation methods and analyses of variance techniques. During this fiscal year, 100 sets of twins residing in Southern California were examined through contracts with Mt. Zion Hospital and University of California at Davis with a subcontract to the Rancho Los Amigos Hospital in Los Angeles and 70 sets of twins from Indiana were examined through a contract with the University of Indiana as follows:

Serial No. NHLI-FERS-1
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

NHLI San Francisco Area Twin Study
Principal Investigator: Ray H. Rosenman, M.D.
Contract Amount: $11,180

NHLI Sacramento/Davis Area Twin Study
Principal Investigator: Nemat O. Borhani, M.D.
Contract Amount: $6,321

NHLI Los Angeles Area Twin Study
Principal Investigators: Nemat O. Borhani, M.D.
Ronald Selvester, M.D.
Subcontract amount: $33,600

NHLI Midwest Area Twin Study
Principal Investigator: Joe C. Christian, M.D.
Contract Amount: $45,997

Major Findings: Preliminary results to date indicate major genetic determinants of the observed variability in height, weight, and serum cholesterol levels, moderate genetic effects on blood pressure, and virtually no genetic component for the variability in serum triglycerides. Analysis of the dietary records of the twins in New England and Washington, D.C. area suggest that several components of the dietary intake may be in part genetically determined. These analyses constitute a doctoral thesis by Miss Marthana Hjortland submitted to the University of Minnesota.

Significance to Bio-medical Research and the Program of the Institute: Despite a growing awareness of the importance of genetic factors in CVD there have been relatively few studies in this area. It is recognized that twin studies are potentially the most powerful available for studying genetic factors in human disease. The present study takes advantage of the largest population of male twins yet assembled to study this important question in relation to cardiovascular diseases.

Proposed Course of Project: Data tapes have been prepared for the 200 sets of twins examined in New England, Northern California, and the Washington, D. C. area. Analyses are proceeding on these data. During the next fiscal year, the California investigator will endeavor to examine an additional 100 sets of twins in Southern California. Extension of the contract to the University of Indiana will permit the examination of another 100 sets of twins in Indiana and nearby Ohio and Kentucky. Analyses will be performed during the next fiscal year on the data on the first 500 twin sets.

Serial No. NHLI-FERS-2
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Analysis of Framingham Heart Study Data

Previous Serial Number: NHLI-FERS-2

Principal Investigator: Manning Feinleib, M.D. (This refers to FERS service)

Other Investigators: William B. Kannel, M.D.
Tavia Gordon
Max Halperin, Ph.D.
Robert J. Garrison, M.S.
Robert C. Brasch, M.D.

Cooperating Units: Framingham Heart Study, NHLI
Biometrics Research Branch, NHLI

Man Years

Total:	1.0
Professional:	0.8
Other:	0.2

Project Description:

Objective: The Framingham Heart Study is a long-term prospective study to elucidate the role of various risk factors in the incidence and natural history of cardiovascular disease. During the past 20 years, a vast amount of data has been collected. In cooperation with the Framingham Heart Study and the Biometrics Research Branch of the NHLI, the FERS is assisting in the analysis of certain portions of this data. The major areas that members of the FERS are concerned with are:

1) The natural history of risk factors including hypertension, obesity, and hypercholesterolemia.
2) The natural history of coronary heart disease including studies of subsequent morbidity and survival.
3) Autopsy correlation with selected risk factors and premorbid ECG findings.
4) Familial and spouse aggregation of CHD and associated risk factors.
5) Cancer and other disease end points.
6) Ascertainment of morbidity status of patients missing recent Framingham examinations.

Serial No. NHLI-FERS-2
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Methods Employed: New techniques are being developed to analyze longitudinal data. These include application of the theory of stochastic processes and regression procedures. Genetic models are being applied to existing familial data.

Major Findings:

1) A study of correlations of risk factors among siblings and spouses has been underway. The sib analyses indicate significant familial association of serum cholesterol, relative weight, blood pressure and smoking habits. These correlations tend to remain stable during middle age when most of the sibs are living apart and thus experiencing somewhat different environmental conditions. This is consistent with the hypothesis that variations in risk factor levels observed in mid-life are largely due to genetic effects or environmental differences operating at younger ages.

2) An analysis of special examinations performed by local physicians of Framingham subjects who had left Framingham and missed the standard examinations at the Heart Study facilities revealed relatively low rates of disease end-points that had not previously been known to the Study. This indicates that the results reported in the several Framingham reports are not significantly biased by selective losses to follow-up.

Significance to Bio-medical Research and the Program of the Institute: All of the goals of these analyses are of vital importance to the understanding of the causes and course of heart disease. Many of these analyses have had to await the accumulation of adequate numbers of cases to provide meaningful rates and comparisons. It is anticipated that the results of these analyses will provide essential information for guiding further research and program planning.

Proposed Course of Project: These analyses and follow-up studies will continue to be pursued during the forthcoming year. Several manuscripts have been completed and others are in preparation for publication and presentation.

Serial No. NHLI-FERS-3
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Framingham Cardiovascular Disease Survey

Previous Serial Number: NHLI-FERS-3

Principal Investigator: Manning Feinleib, M.D.

Other Investigators: Robert C. Brasch, M.D.
James Margolis, M.D.
William B. Kannel, M.D.

Cooperating Units: Framingham Heart Study

Man Years

Total:	0.9
Professional:	0.9
Other:	-

Project Description:

Objective: This study is a twelve month mortality and morbidity survey of the town of Framingham, Massachusetts, to determine all new episodes of cardiovascular disease in this defined population. The estimates of incidence and mortality of CVD obtained from this "cross-sectional" survey will be compared with the rates obtained from the longitudinal data from the Framingham Heart Study which has followed a subsegment of the town of Framingham for the last 20 years. As part of the documentation of each new event details are obtained about prodromal and precipitating factors in cardiovascular disease as well as the resources used by the patients to obtain medical care.

Methods Employed: Data on mortality and morbidity are obtained from three sources: (1) death certificate records, (2) surveillance of local hospitals and nursing homes and the major hospitals in surrounding communities and (3) periodic survey of all physicians in the community. Data on the prodromal cause and confirmation of the nature of the event are obtained from two further sources: (1) personal interview and examining of surviving patients, and (3) interview of spouse, other relatives or friends of the CVD patients.

Major Findings: Preliminary results indicate that the incidence of major cardiovascular events in the total community is similar to that obtained in the longitudinal study.

"Softer" endpoints such as angina pectoris and congestive failure have yielded different rates, AP is reported less frequently by the practicing physicians while CHF is diagnosed more often than was predicted. It was further found that the major source of delay in obtaining care for acute coronary events was due to patient indecision.

Significance to Bio-medical Research and the Program of the Institute: Cardiovascular diseases are by far the leading causes of morbidity and mortality among adult men and women in the United States. Despite the vast importance of these diseases it has been difficult to obtain accurate estimates of their total impact. This is due to the fact that the recognition and reporting of cardiovascular diseases are highly sensitive to the survey methods used, the criteria of definition of disease, the level of medical care in the community, and the health consciousness of the population. In the past two decades there have been several cross-sectional studies of cardiovascular disease in defined communities as well as several prospective studies following samples of the population. Not surprisingly these have resulted in widely varying estimates of the incidence and mortality from these diseases. Since each of these studies was done by different investigators using somewhat different techniques and criteria for definition it is difficult to assess to what extent the differences in rates are due to the methodology of studying the diseases or are due to real differences in the rates within the defined populations. One way to avoid this difficulty is to do a study in a definited population by two different techniques using comparable methods and criteria. This is the study which is being conducted in the Framingham area.

Proposed Course of Project: The survey was launched in June, 1970. Through June, 1971, there were 237 cardiovascular episodes reported. During the current year, all hospitals in Massachusetts and all nursing homes in the Framingham area were contacted and their records reviewed for eligible survey patients. Most of these reviews were facilitated by the availability of computerized files at most of the institutions, but many required hand searches. An additional 100 possible cases were picked up by this effort. A standardized review of all eligible patients is underway and will be completed during the next 6 months with analyses to follow thereafter.

Serial No. NHLI-FERS-4
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Medical Facility Utilization During Acute Coronary Episodes

Previous Serial Number: NHLI-FERS-4

Principal Investigator: Manning Feinleib, M.D.

Other Investigators: Robert J. Garrison, M.S.
Arthur Simon, M.D.
Angelo Alonzo, M.A.
Michael J. Davidson, M.D.

Cooperating Units: Montgomery County Health Department
Holy Cross Hospital
Maryland State Department of Vital Statistics

Man Years

Total:	0.2
Professional:	0.2
Other:	-

Project Description:

Objective: To describe the course of action taken by persons experiencing acute coronary episodes and to distinguish physiological, social, cultural or geographic factors that may have influenced the course of events

Methods Employed: The admission records of Holy Cross Hospital were systematically searched for cases admitted between January 18, 1969, and January 17, 1970, for which the preliminary diagnosis was acute coronary heart disease. If a patient resided in one of twenty-five previously defined census tracts surrounding Holy Cross Hospital an interview with the patient and those present at the time of his episode was subsequently obtained. Death certificates from the Montgomery County Health Department were also searched for persons meeting the above residence and date of death requirements whose primary cause of death was listed as coronary heart disease. The decedent's physician and immediate family were interviewed in an attempt to obtain as much information as possible as to the circumstances surrounding the death.

Serial No. NHLI-FERS-4
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Major Findings:

1) A mortality survey of all deaths in 25 census tracts of Montgomery County, Maryland, in 1969 revealed that more than 60% of the total CHD mortality occurred outside of a hospital and that for those who died after being admitted to a local hospital, the median delay from onset of symptoms until hospital arrival was 5.6 hours.

2) An analysis of patients' responses to acute episodes of CHD reveals that a vast variety of methods are employed to cope with the presenting symptoms. Most patients will decrease their activities in an effort to diagnose their condition or seek symptom relief. There was no correlation between the frequency and types of self-treatment methods and several demographic variables indicating that the patients' responses are governed primarily by the nature and severity of symptoms and "situational" factors rather than by stereotyped or predetermined attitudes.

Significance to Bio-medical Research and the Program of the Institute: The utilization of health care facilities in the hours immediately following an acute coronary event hopefully enhances the patient's chances of survival. The present study attempts to elucidate those factors which influence the patient's decision to seek or not to seek medical attention in the hours following the onset of coronary symptoms. Particular attention has been given to the differences between in-hospital patients and those who died without reaching the hospital with a view to possible intervention. The study's findings will perhaps allow a more systematic approach to the problem of health care utilization during acute episodes of heart disease.

Proposed Course of Project: Data acquisition on 293 in-hospital patients and 142 outside hospital deaths has been completed. Analysis has been completed on four studies of prodromal symptoms and out of hospital deaths and manuscripts have been prepared. Further analyses will be pursued during the next fiscal year.

Serial No. NHLI-FERS-5
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Framingham Offspring Study

Previous Serial Number: ----

Principal Investigator: Manning Feinleib, M.D.

Other Investigators: William B. Kannel, M.D.
William P. Castelli, M.D.
Robert M. McNamara
Robert J. Garrison, M.S.

Cooperating Units: Framingham Heart Study
Framingham Union Hospital

Man Years (FERS only)

Total:	0.9
Professional:	0.9
Other:	-

Project Description:

Objective: To study the familial aggregation of cardiovascular risk factors and the occurrence of CVD in the offspring of the 1644 spouse pairs who were included in the original Framingham cohort and to elucidate secular trends in risk factor levels and disease incidence.

Methods Employed: Among the 5209 subjects in the original Framingham cohort established in 1948-52, there were 1644 spouse pairs (3788 individuals) who had approximately 4,000 children who were too young to be included in the original chort. A roster of these offspring is being prepared and the children are being invited to undergo the same examination that their parents have had at each of their biennial examinations. The Framingham Heart Study staff performs these examinations as described in the reports of that section. Supporting laboratory and technical services are provided by the Framingham Union Hospital under a contract as follows:

Contract Number:	NIH-70-2243
Program Director:	Luke Tedeschi, M.D.
Contract Amount :	$74,585

Serial No. NHLI-FERS-5
1. Clinical Applications, NHLI
2. Field Epidemiology Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Major Findings: No substantive results are available as yet but the feasibility of the study has been established. About 1000 spouse pairs have been contacted and the names and addresses of their offspring have been obtained. Approximately 1200 of these offspring have been examined during the present fiscal year. In constructing the roster and inviting the cooperation of the offspring it has been found that approximately two-thirds of the offspring of these parents who have taken the most recent Framingham examinations still resided in the Framingham area and their cooperation has been enthusiastic. Approximately 90% of the families have at least one offspring in the Framingham area. On the other hand, those spouses who have not been examined recently due to deaths or migration from Framingham, tend to have very few of their children residing in the Framingham area at present.

Significance to Bio-medical Research and the Program of the Institute: This study has the unique feature of permitting comparisons of two generations of individuals who have been examined by uniform procedures and in whom the younger generation is being examined at about the same ages as their parents were when first examined. The secular trends in cardiovascular risk factors and incidence which have been established during 24 years of observation on the parents' generation will be continued to be studied with their offspring. The familial aggregation of the risk factors will be intensively investigated and sources of individual variation will be further elucidated.

Proposed Course of Project: Completion of the offspring roster and examinations at the Framingham Heart Study facilities will continue during the next fiscal year. Approximately one additional year of examinations will be required to obtain as complete a representation of the available offspring as possible. The roster has been entered on computer tapes and the completed examinations are being edited and processed on a concurrent basis.

Publications

Feinleib M: Venous thrombosis in relation to cigarette smoking, physical activity and seasonal factors. Milbank Memorial Fund Quarterly 50: (No. 1, part 2) 123-141, 1972.

Davidson M and Feinleib M: Carbon disulfide poisoning: A review. Am. Heart J 83:100-114, (Jan) 1972.

Kannel WB and Feinleib M: Natural history of angina pectoris in the Framingham Study: prognosis and survival. Amer J Cardiol 29:154-163, 1972.

Schwartz JT, Reuling FH, Feinleib M, Garrison RJ, and Collie DJ: Twin heritability study of the effect of corticosteroids on intraocular pressure. Journal of Human Genetics In press, 1972.

Feinleib M, Gordon T, Garrison RJ, Kannel WB, Verter JI and Gerende LJ: Blood pressure and age. The Framingham Study. Circulation In press, 1972.

Feinleib M and Davidson MJ: Coronary heart disease mortality A community perspective. J.A.M.A. In press, 1972.

Simon AB, Steinke WE and Curry JJ: Atrioventricular block in acute myocardial infarction. Chest In press, 1972.

Unpublished Papers and Talks

Feinleib M: Length biased sampling and biomedical applications. Discussion of a paper by M. Zelen at the Biometric Society ENAR meeting, Ames, Iowa, April 27, 1972.

Feinleib M: Intervention Studies of Coronary Risk Factors, presented to the Maryland Epidemiologic Society, Baltimore, May 31, 1972.

Schwartz, JT, Reuling FH, Feinleib M, Garrison RJ, and Collie DJ: Twin Heritability Study on the effect of corticosteroids on intra-ocular pressure. Presented at the 7th Joint Meeting of the Clinical Society and Commissioned Officers Association of the United States Public Health Service, New York City, May 31, 1972.

Hjortland MC: The effects of heredity and environment on nutrient intake of adult monozygotic and dizygotic twins. A thesis submitted to the faculty of the Graduate School of the University of Minnesota. June, 1972.

PHS-NIH
NATIONAL HEART AND LUNG INSTITUTE
July 1, 1971 through June 30, 1972

Participation in outside committees and organizations

Manning Feinleib:

was elected to Fellowship in the American College of Preventive Medicine.

served as President of the Society for Epidemiologic Research.

was appointed Chairman of the Publications Committee, Epidemiology Section, American Public Health Association.

was appointed Chairman of the Committee on Criteria and Methods, Epidemiology Council, American Heart Association.

served on the Panel of Advisors of the National Center for Health Statistics.

served as Chairman of an Ad Hoc Scientific Review Committee for the National Institute of Neurologic Disease and Stroke, May 1, 1972.

served on the Etiology Program Advisory Committee, National Cancer Institute.

participated in the Project Areas Planning Session of the National Cancer Plan, Airlie House, December 14-17, 1971.

served on an Ad Hoc Scientific Review Committee for Epidemiologic Studies of Chronic Obstructive Respiratory Diseases, NHLI, May 15, 1972.

served as NHLI representative to the Sixth International Scientific Meeting of the International Epidemiological Association, Primosten, Yugoslavia, August 29-September 4, 1971.

served on a luncheon panel on "Risk Factors and Development of Coronary Artery Disease" at the 37th Annual Meeting of the American College of Chest Physicians, Philadelphia, October 28, 1971.

served on a Workshop on Lower Limb Venography, Bethesda, December 13-14, 1971.

served as an editorial reviewer for the American Journal of Epidemiology, Cancer Research, and HSMHA Health Reports.

Serial No. NHLI-BRB
1: Clinical Applications
2. Geographical Diseases
3. Jerusalem, Israel and
Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Israel-United States Cooperative Ischemic Heart Disease Study

Previous Serial Number: NHLI-BRB

Principal Investigator: Jack H. Medalie, M.B., Ch.B., M.P.H., Professor and Chairman, Dept. of Family Medicine, Tel-Aviv University Medical School, Tel Hashomer, Israel

Project Officer: William J. Zukel, M.D., D.P.H., Associate Director for Clinical Applications, NHLI

Other Investigators: Henry N. Neufeld, M.D., Chief, Heart Institute, Tel-Aviv
Egon Riss, M.D., M.Sc., Director, Heart Institute, Haifa
Tavia Gordon, Supervisory Statistician, NHLI

Cooperating Units: National Heart and Lung Institute
Hadassah Medical Organization
Ministry of Health, Government of Israel
Hebrew University-Hadassah Medical School

Man Years: Total NHLI: .3
Professional .3
Other: -

Project Description:

Objectives: This is a prospective epidemiological study of hypertension and ischemic heart disease in a defined segment of male government and municipal employees of Israel. This population represents diverse ethnic and geographic origins and differs in prevalence of cardiovascular disease.

The objectives of the study are to determine the biologic characteristics including physical measurements, biochemical, dietary and psychosocial measurements upon an adequate population sample size to allow the ascertainment of incidence of morbidity and mortality from ischemic heart disease and hypertension in relation to the measured characteristics.

Serial No. NHLI-BRB
1. Clinical Applications
2. Geographical Diseases
3. Jerusalem, Israel and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Methods Employed: The study population consists of 10,232 male Israeli Civil Servants age 40 and over representing approximately 1500 subjects from each of six geographical regions, Eastern Europe, Central Europe, Southwestern Europe, Middle East, North Africa and Israel native-born.

A prevalence phase baseline examination was conducted in 1963 comprising an extensive battery of standardized physical, laboratory, dietary, and psychosocial measurements. 86.2 per cent of the invited individuals were examined. The 1644 non-respondents did not differ appreciably in age or place of birth from the respondents.

The population has received two re-examinations, one in 1965 and one in 1968 with a response rate of over 95% on both occasions. The period between examinations has been marked by intensive morbidity and mortality follow-up of all subjects.

Progress to June 1972: All basic data have been edited and placed on computer tape. A series of tabulations are systematically being produced to look at univariate and multivariate risk factor relationships to incidence of ischemic heart disease, hypertension, diabetes, peripheral vascular disease and also analysis of data on pulmonary function measurements.

The main topics of analysis with preparation for publication are listed below:

Plan for Data Analysis and Reports in Respect to 5-Year Incidence Data

Content Areas	Completion of Reports (papers) 1971	1972	1973-74
I. Myocardial Infarction			
1. Incidence and mortality experience	S		
2. Univariate associated factors	S		
3. Multivariate analysis-clinical infarcts		M	
4. "Silent" infarcts-multivariate analysis		M	
5. Sudden deaths		M	
6. The Yemenites (low incidence)		M	
7. The Religious Subjects (low incidence)		M	
8. Comparison of computer and cardiologists in respect to ECG's			

Serial No. NHLI-BRB
1. Clinical Applications
2. Geographical Diseases
3. Jerusalem, Israel and Bethesda, Maryland

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Individual Project Report
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Content Areas	Completion of Reports (papers) 1971	1972	1973-74
II. Angina Pectoris			
1. Incidence	M		
2. Univariate analysis		M	
3. Multivariate analysis			
4. Others, arising out of 1, 2, and 3			
III. Blood Pressure and Hypertension			
1. Distribution and (multivariate)	P		
2. Incidence and associated factors (WHO def.)	A		
3. Multivariate analysis			
4. Others			
IV. Diabetes Mellitus			
1. 2- year incidence	P		
2. 2- year multivariate analysis	P		
3. 5- year incidence		M	
4. 5- year univariate		M	
5. 5- year multivariate			
6. Follow-up of subsample+blood insulin levels		M	
7. Others			
V. Blood Groups			
1. And cholesterol	P		
2. And myocardial infarction/angina pectoris	P		
3. And hypertension/peripheral vascular disease		S	
4. And diabetes/peptic ulcer			
VI. Peptic Ulcer			
1. Incidence	S		
2. Univariate analysis			
3. Multivariate analysis			
VII. Peripheral Vascular Disease			
1. Incidence			
2. Univariate analysis			
3. Multivariate analysis			
VIII. Sociological Data			
1. Sociological Fact Book	Hebrew Edition M	English Version M	
2. Others			

Serial No. NHLI-BRB
1. Clinical Applications
2. Geographical Diseases
3. Jerusalem, Israel and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Content Areas	Completion of Reports (papers) 1971	1972	1973-74
IX. Psychosocial Aspects			
1. Psychosocial aspects as related to major diagnoses			
2. Concentration camp experience			
X. Miscellaneous			
1. Other genetic markers: G6PD/Pseudocholineresterase		P	
2. Conjunctival micropools		M	
3. Fundograms			
4. Sibling study of 300 study subjects who are in the U.S.A.		M	
XI. Cerebro-Vascular Accidents			
1. Incidence and associated factors			
XII. Respiratory Function Tests			
1. Distribution by age and birthplace	A		
2. Association with previous morbidity and characteristics of population			
3. Nomograms of examined population		S	
XIII. Relationship Between Physical Activity and Physical Fitness		M	
XIV. Comparison of Prevalence and Incidence			
XV. Comprehensive "Tie-up" and Summary of the Epidemiology of Ischemic Heart Disease with Its Implications for Clinical Practice and Preventive Programs			

S = Submitted for Publication
M = Manuscript Prepared
P = Published
A = Accepted for Publication

Serial No. NHLI-BRB
1. Clinical Applications
2. Geographical Diseases
3. Jerusalem, Israel and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Significance to Bio-medical Research and the Program of the Institute: This large prospective study of coronary heart disease in Israel affords an opportunity to investigate whether factors established as related to CHD risk elsewhere are also important in this heterogenous population; to investigate the importance of other factors such as psychosocial stress and diet and to evaluate whether great differences in "way of life" 10 or more years prior to the current observations are related to important differences in incidence of CHD. Migration patterns have produced a unique natural experiment for testing a number of hypotheses relating to CHD with methodology comparable to the Framingham Study.

Proposed Course of the Project: The available funds are being used so as to permit maximum tabulation and analysis of this rich body of data. Mr. Tavia Gordon is continuing the statistical consultation for planning further tabulations and analysis of the sizable remaining data.

Since the analysis work yet to be done cannot be accomplished during calendar year 1972 within the remaining P.L. 480 funds, some mechanism of further support for the statistical group in Israel will be necessary for one more year to produce full analysis of the extensive data from this study.

Publications:

Kahn, H.A. et al.: Factors related to diabetes incidence: A multivariate analysis of two years observation on 10,000 men. J.Chr.Dis.23: 617-629, 1971.

Sive, P.H. et al.: Distribution and multiple regression analysis of blood pressure in 10,000 Israeli men. Am.J. Epid.93: 317-327, 1971.

Neufeld, H.N. et al.: The use of a computerized ECG interpretation system in an epidemiologic study. Meth. Inform. Med. 10: 85-90, 1971.

Serial No. NHLI-BRB
1. Clinical Applications
2. Geographical Diseases
3. Zagreb, Yugoslavia

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Epidemiological Investigation of Ischemic Heart Disease and Hypertension in Yugoslavia

Previous Serial Number: NHLI-BRB

Principal Investigator: Bojan Pirc, M.D., Professor of Biostatistics, Andrija Stampar School of Public Health, University of Zagreb

Co-Investigator: Djordje Kozarevic, M.D., M.P.H., Chief, Chronic Diseases Program, Fed. Inst. Pub. Health, Belgrade

Project Officer: William J. Zukel, M.D., D.P.H., Associate Director for Clinical Applications, NHLI

Other Investigators: Danimir Bartolivic, M.D., Director of Public Health, Remetinec; P. Shalek, M.D., Cardiologist, Zagreb; Sulejman Azabagic, M.D., Director of Pub. Health, Tuzla; M. Strasser, M.D., Cardiologist, Tuzla; Dr. Josipovic, Cardiologist, Tuzla; Tavia Gordon, Supervisory Stat., NHLI; T.R. Dawber, M.D., Consultant, NHLI; Albert Roberts, M.D., Consultant for Respiratory Studies, NHLI

Cooperating Units:
National Heart and Lung Institute
Federal Institute of Public Health, Belgrade
Health Statistics Center, Belgrade
Public Health Center, Remetinec
Mayo and Council of Remetinec
Institute of Hygiene, Zagreb
School of Public Health, Zagreb
Institute of Hygiene, Ljubljana
Public Health Center, Tuzla
Hospitals and Medical Care Department, Tuzla
Mayor and Council of Tuzla Commune

Man Years:

Total:	.25
Professional:	.25
Other	-

Serial No. NHLI-BRB
1. Clinical Applications
2. Geographical Diseases
3. Zagreb, Yugoslavia

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Description:

Objectives: The specific objective of this study is to determine the incidence of different forms of cardiovascular diseases in rural and industrial populations and the relationship between incidence rates and ethnic origin, diet, type of work, physical activity, body type, and personal habits such as the use of tobacco and alcohol. The principal cardiovascular diseases studied will be hypertension and coronary (ischemic) heart disease. The primary emphasis will be upon the study of the incidence of these forms of cardiovascular disease in newly industrialized populations. A unique opportunity exists in Yugoslavia to study the incidence of cardiovascular diseases in a rural population as it becomes industrialized.

Methods Employed: Selection of two cities with desired population characteristics was made and the groundwork of establishing medical and community acceptance was carried out in Remetinec near Zagreb and Tuzla in the mountains southwest of Belgrade.

A census of men aged 35 to 64 was conducted identifying 6,856 eligible subjects in Tuzla, the Moslem community and 5,018 eligible subjects in Remetinec, the Christian community.

An epidemiological study plan adapted to local circumstances was drawn up with central elements of comparability to the Framingham Study. This standardized protocol was developed and pretested. Staff were trained and interstudy comparability established including arrangements for central laboratory processing of blood for biochemical determinations.

The first examination cycle was completed in 1964 attaining 94% of the eligible subjects of Tuzla and 92% of eligible subjects in Remetinec. The second examination cycle was conducted in 1966-67 and more than 90% of the original subjects were re-examined. The health status of living non-respondents has been established to some degree so that some information on the complete cohort is available.

Serial No. NHLI-BRB
1. Clinical Applications
2. Geographical Diseases
3. Zagreb, Yugoslavia

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Progress to June 1972: Final diagnoses for the second examination and for interim morbidity and mortality have been established and the incidence of myocardial infarction calculated. Morbidity and mortality follow-up continue and the final re-examination cycle began in May 1971.

During 1971-72 the cardiovascular examinations under the prescribed protocol were completed on 3,200 of the participating cohort subjects in Tuzla and 1,900 men were re-examined within the Remetinec population.

The protocol for the respiratory disease study was completed and the respiratory components will become the major area of future emphasis as the cardiovascular disease study comes to completion with the end of the present third incidence cycle.

Major Findings: The annual incidence of myocardial infarction and coronary heart disease death within this study population aged 45-62 was established to be 1.8 per 1,000 in comparison with the Framingham rate of 9.4 per 1,000 or an incidence of 19% of the comparable Framingham rate.

Risk factor associations cannot yet be established from the small number of incidence cases. This will be done when the data from the present Exam III cycle are completed within the next year.

Significance to Bio-medical Research and the Program of the Institute: Having identified the very low rate of myocardial infarction incidence experienced by these populations we now have the opportunity to search for possible protective factors in this population. The additional finding of high prevalence of pulmonary disease provides an opportunity to study the epidemiology of chronic obstructive lung disease.

Proposed Course of Project: A visit to the project was made in September 1971 to review progress in the final examination cycle. ECG readings and a systematic review of all incidence cases were carried out by Dr. Dawber to make diagnostic readings comparable to Framingham.

The major objectives of the project should be attained with the expected completion of the follow-up and re-examination of living subjects through the Exam III cycle. The high incidence of respiratory disease has resulted in the establishment of a new study based upon the extensive population data acquired in the CVD study.

Depletion of P.L. 480 funds in Yugoslavia will prevent planning of new projects and priority will be given to complete the presently approved CVD and respiratory disease studies.

Serial No. NHLI-BRB
1, Clinical Applications
2. Geographical Diseases
3. Zagreb, Yugoslavia

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Publications:

Kozarevic, D. et al.: Prevalence and incidence of coronary disease in a population study. The Yugoslavia Cardiovascular Disease Study. J. Chr. Dis. 24: 495-505, 1971.

Pirc, B. et al.: The epidemiologic study of cardiovascular diseases in Yugoslavia. Methodology with special reference to Third Examination.

Kozarevic, D., Roberts, A. and Pirc, B.: Prevalence of chronic obstructive lung diseases among rural and urban populations in two different areas of Yugoslavia.

Serial No._____
1. Clinical Applications
2. Geographical Diseases
3. Honolulu, Hawaii

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Honolulu Heart Disease Epidemiology Study

Previous Serial Number:

Principal Investigator: Abraham Kagan, M.D.

Other Investigators:
Gary Glober, M.D.
Grant N. Stemmermann, M.D.
Robert M. Worth, M.D.
Stephen M. Peskoe, M.D.
Joseph Moore, M.D.
Christian L. Gulbrandsen, M.D.
Takuji Hayashi, M.D.
Jordan S. Popper, M.D.
Tavia Gordon

Co-operating Units:
University of Hawaii
Kuakini Hospital
Atomic Bomb Casualty Commission, Hiroshima
University of California School of Public Health, Berkeley
Community Medicine Program, San Francisco
National Cancer Institute

Man Years:

Total:	11
Professional:	3
Other:	8

Project Description and Objectives:

The reported coronary heart disease mortality rate of men of Japanese descent in the United States is two to three times as great as that of men of the same age in Japan. Conversely, the cerebrovascular disease mortality rate in Japan exceeds that in the United States. This difference in mortality experience in two groups of men of similar ethnic origin is evidence for the importance of some environmental factor(s) in the causation of these diseases.

The purpose of the present project, being carried out in co-operation with the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki, Japan, with the University of California School of Public Health, Berkeley, and with the Community Medicine Program, San Francisco, is, first, to test and assess carefully the degree of these reported differences in disease experience with regard to morbidity as well as mortality, and, second, to delineate the environmental factor(s) responsible for the differences.

Methods Employed

Parallel studies began in Honolulu and in Hiroshima-Nagasaki in January 1965, utilizing comparable self-administered questionnaires specifically devised for the purpose. The study cohort in Hawaii was identified expeditiously through Selective Service registration records, the addresses being updated by the use of business and telephone directories and of State agency rolls. Because of Hawaii's geography and the United States' immigration policy, in- and out-migration of Japanese men has been relatively small, and these men are therefore well defined by the thorough Selective Service registration which occurred during the early 1940's.

The first phase of the study, collection of data by a self-administered questionnaire, was completed in late 1965. Of the total 12,417 questionnaires which were mailed out, 1,269 were returned unlocated, and 1,270 men refused to answer the questionnaire. The 9,878 men who completed and returned questionnaires constituted the cohort which was to be examined.

This examination, the second phase of the study, began in late October 1965. In addition to routine cardiovascular measures, the subjects were characterized according to a 24-hour diet history, various anthropometric variables, and detailed blood measurements. Serum was analyzed for glucose one hour after a 50 gram glucose load, for uric acid, for cholesterol, and for triglyceride.

The first examination of the cohort was completed in November 1968, with the examination of 8,006 subjects. A comparable examination cycle in Hiroshima-Nagasaki required only two years, and in California, through the use of the Kaiser multiphasic screening facilities, the examination cycle was completed in August 1970, less than one year after its start.

Re-examinations were initiated in October 1967, with the examination format altered by the omission of the 24-hour diet history and the addition of a brief, structured screening neurological examination. A repeat electrocardiogram was done. Blood was drawn on all the subjects and determinations of

hematocrit, cholesterol, glucose (without a glucose load), uric acid, and triglyceride were performed on a 20% sample. Serum samples of the rest were frozen for future determinations. This second cycle of examinations at Honolulu was completed in November, 1970. 7,498 or 94% of the examinees returned for examination two years following the first. Eighty-two men died within 24 months of their initial examinations. Of the 426 survivors who failed to return, contact has been made with 403; 390 were reportedly free of coronary heart disease and of cerebrovascular disease in the two years following their first examination. Five had documented myocardial infarctions and eight had documented strokes. Twenty-three men have not yet been contacted and are thus far lost to follow-up, although they are believed to be alive.

Our consultant neurologist, Dr. Popper, has been examining all those individuals picked up on the screening neurological examination as showing suspicious evidence of cerebrovascular accidents. The findings of this detailed neurological examination will be used to determine prevalence of stroke in our cohort as well as to eliminate people from the population-at-risk of developing new stroke, to be determined in the third cycle of examinations, again by screening followed by definitive examinations.

Serum samples and electrocardiograms have been interchanged with the Hiroshima investigators; and staff pathologists from both Hiroshima and Honolulu are independently grading the atherosclerotic lesions in necropsy material from both areas. In addition, electrocardiograms from all three study sites were mounted on identical forms and Xerox copies of these electrocardiograms were interpreted and coded by trained personnel in the laboratory of Dr. Henry Blackburn in Minneapolis.

A number of substudies have been performed. During the second examination, data were gathered relative to chronic broncho-pulmonary disease. Spirograms were recorded on all examinees; sputum was collected on those who complained of chronic, productive cough; and in a series of subjects with evidence of chronic, obstructive lung disease, and in a number of controls, a determination of Alpha-1 antitrypsin level was performed. In conjunction with Mainland centers, data were collected on precursors of acute myocardial infarction and sudden death. Data collection for this study was completed in December. We have been participating in the co-operative lipoprotein phenotyping project. The collection of plasma and serum for this study will have been completed by June, 1972 with specimens obtained from 2,900 men, or 85% of the selected sample of 3,400.

Dr. Syme of the California study has designed an acculturation questionnaire to assess the degree of westernization of Japanese-Americans living in California. The need for such data arose from the hypothesis that adoption of the "American way of life" may alter the disease experience of Japanese in the United States compared to those of Japan through a mechanism independent of diet or other usually measured behavioral variables. This concept is supported by the demonstrated difference in incidence of and mortality from coronary heart disease in age-matched Issei and Nisei living in Hawaii. It was, therefore, decided to apply this questionnaire to the Honolulu Heart Study cohort. Mailing of the questionnaires began in July 1971 and by mid-March 1972, of the 7,563 questionnaires which were mailed, 4,672 were returned for a response rate of 61%. Keypunching and analysis of these data will be performed at the University of California in Berkeley.

Starting in October 1971, a third cycle of examinations was started in conjunction with the National Cancer Institute. The men are being recalled for examination near the sixth anniversary of their initial examination. The cardiovascular portion of the examination is directed primarily at the detection of new events of coronary heart disease and stroke occurring in the interim since the previous examination four years before. In addition, determinationsof Alpha-1 antitrypsin levels and Pi phenotypes are being performed; and detailed investigation of pulmonary function on a selected sample of individuals will be performed according to a protocol devised by Dr. Roberts.

Surveillance of hospitalizations and deaths in the study subjects has continued. This surveillance is being maintained on all Japanese men living on Oahu, born between 1900 and 1919, whether or not they responded to the initial questionnaire or were examined, in order to compare the morbidity and mortality experience of respondents and nonrespondents. Using detailed, pretested criteria, the staff medical record librarian carefully screens all Oahu hospital discharge records and death certificates, and these records are then regularly reviewed by staff epidemiologists who assign most probable diagnoses in each case. In addition, the staff pathologist participates in the majority of necropsies on these men, using standardized methods for grading atherosclerotic lesions.

Major Findings

A comparison of the characteristics of the three Japanese populations under study reveals that the Hawaiians closely resemble the Californians in height, weight, skinfold thickness, hematocrit, and uric acid. In both of these American cohorts, the men are only slightly taller than those in Japan; in the other variables, the American measurements are substantially greater than those in Japan. The Hawaiian cohort resembles the

Japanese in measures of ventilation, both in terms of total forced expiratory volume and in the one second forced expiratory volume, expressed as a per cent of the total. They also resemble each other in systolic and diastolic blood pressures. In these measures, the California values are higher than in the other two cohorts. Hawaiian serum glucose values are slightly higher than Californian which are, in turn, slightly higher than those in Japan; the most striking difference is between Hawaiian and Japanese men in the older age groups. California cholesterol values are slightly higher than Hawaiian which are, in turn, much higher than those in Japan.

The major dietary differences between the indigenous and migrant Japanese are in the preponderance in the diet in Japan of complex carbohydrates, primarily in the form of rice, and the lower intake there of fat. Both the Hawaiian and the Californian Japanese diet is characterized by its higher intake of animal protein, simple sugars, and fat. Thirty-three per cent of calories in Hawaii and 38% in California is in the form of fat with a preponderance of saturated fat.

A substudy has been performed on samples of men both in Japan and in Hawaii, stratified according to serum cholesterol levels, to determine more quantitatively their dietary intake by means of a 7-day diet record. These studies have substantiated the findings according to the 24-hour recall method. Volunteers among these men in Hawaii have had a needle aspiration of subcutaneous adipose tissue for analysis of the fatty acid composition by gas chromatography.

The prevalence of coronary heart disease at the first examination was analyzed, using the categories for which data are available in published material from Framingham and from the Atomic Bomb Casualty Commission. Combining subjects with definite or possible electrocardiographic evidence of myocardial infarction and those with angina pectoris, a total prevalence of 32.3 per thousand was obtained for Honolulu. This compared with rates of 47.2 and 18.2 per thousand for Framingham and Japan, respectively. These differences were statistically significant and not explained by age differences. Analysis limited to cases with definite electrocardiographic evidence of prior myocardial infarction showed the same trends but the differences were not statistically significant.

One hundred and one men developed new coronary heart disease during the two years following their first examination. The annual incidence rate ranged from 2.5 per thousand in those aged 45 to 49 to 11.7 per thousand in those aged 65 to 68. Here, again, the rates are intermediate between those in Japan and those in Framingham. Age-adjusted means for selected variables were contrasted for the subjects developing coronary heart disease and

for the rest of the population-at-risk. The most significant difference was the higher systolic blood pressure in the cases. Also significantly greater among the cases were various measures of adiposity, such as skinfold measurements, and casual cholesterol and triglyceride levels. There was no difference between the serum glucose levels of the two groups. In a discriminant function analysis, age, sum of skinfolds, cigarette smoking, systolic blood pressure, and cholesterol were found to be statistically significant predictors of coronary heart disease incidence in this Hawaiian cohort. Comparison of incidence among Issei (those born in Japan) and among Nisei (men born in Hawaii of Issei parents) shows a consistently higher incidence rate among the Nisei despite insignificant differences in various measured risk factors. At comparable risk factor levels, the incidence of coronary heart disease among Hawaiian Japanese males as a whole is approximately half that of Caucasian males of the Framingham population.

Between 1965 and 1970, among those Hawaiian Japanese males who had been born between 1900 and 1919, 756 died. According to the death certificates, 27% died of coronary heart disease and 13% died of cerebrovascular accidents. Of these deaths, 372 or 49% came to autopsy. In these, the cause of death was attributed to coronary heart disease in 22% and to cerebrovascular accidents in 12%.

Proposed Course

Third cycle examinations will continue near the sixth anniversary date of the first examination. The emphasis is on the detection of interim coronary heart disease and interim stroke, the latter by an examination by our consultant neurologist of anyone picked up by the screening examination. The objective will be to develop more precise age-specific incidence rates for coronary heart disease in general, as well as age-specific rates for different manifestations of coronary heart disease, especially of hard, documented cases of myocardial infarction. Such rates developed through examination will be more comparable with the rates developed in Hiroshima and in Framingham and in other Mainland cardiovascular disease study centers than are rates which can be determined by surveillance, alone. In the two-year incidence follow-up, only 28 new cases of stroke were detected in our population-at-risk. With the population now older and with six years of follow-up compared to two, we anticipate that it may be possible to relate stroke incidence also to risk variables in the study cohort.

In the coming year data for analysis will become available from the lipoprotein phenotyping project and from the study on acculturation.

Surveillance of the members of the cohort for development of lethal and nonlethal cardiovascular and cerebrovascular disease will continue. Diagnostic criteria for morbidity and mortality have been pretested extensively. In all centers, the 8th Revision of the International Classification of Diseases and Causes of Death is used to ensure comparability with the other studies; and common methods of data processing, tabulation, and analysis have been developed and agreed upon.

Publications:

Gould, S.E., Hayashi, T., Tashiro, T., Tanimura, A., Nakashima, T., Shohoji, T., and Ashley, F.W.: Coronary Heart Disease and Stroke. Atherosclerosis in Japanese Men in Hiroshima, Japan, and Honolulu, Hawaii. Arch. Path. 93: 98-102, 1972.

Kagan, A., Rhoads, G.G., Zeegen, P.D., and Nichaman, M.Z.: Coronary Heart Disease Among Men of Japanese Ancestry in Hawaii: The Honolulu Heart Study. Israel J. Med. Sci. 7: 1573-1577, 1971.

Kagan, A.: Cancer Mortality Among Ethnic Groups in Hawaii. Israel J. Med. Sci. 7: 1451-1454, 1971.

Serial No. NHLI
1. Clinical Applications
2. Geographical Diseases
3. San Juan, Puerto Rico and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Epidemiological Study of Coronary Atherosclerosis in Puerto Rico

Previous Serial Number: NHLI

Principal Investigator: Mario R. Garcia-Palmieri, M.D., Professor and Head, Department of Medicine, University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Project Officer: William J. Zukel, M.D., D.P.H., Associate Director for Clinical Applications, NHLI

Other Investigators: Raul Costas, M.D., Asst. Prof. Med.; Mercedes Cruz Vidal, M.D., Med. Instr.; Mercelino Cortes, M.D., Assoc. Med.; Dr. Patterne (½ time); Emilio Nazario, Sup. Tech.

NHLI: Joyce Schiffman, Stat. Consult.
Jeanne Tillotson, Nutr. Consult.
William B. Kannel, M.D., Med. Liaison, Framingham
Albert Roberts, M.D., Pul. Dis. Consult.

Cooperating Units: National Heart and Lung Institute
University of Puerto Rico School of Medicine
Department of Public Health
Office of Census, Puerto Rico Planning Board
Information Processing Division, Medical Center
Medico-Legal Institute
Municipalities of Bayamon, Guaynabo, Carolina, Catano (urban), Naranjito, Comerio, Corozal, Cidra, Aguas Buenas, Barranguitas (rural)

Man Years: Total NHLI:
Professional 3/4
Other -

Serial No. NHLI
1. Clinical Applications
2. Geographical Diseases
3. San Juan, Puerto Rico and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Description:

Objectives: To determine the factors which are significantly associated with an unusually low death rate from coronary heart disease and a reduced severity of coronary atherosclerosis found on autopsy among men age 45-64 living in Puerto Rico. Pilot investigations confirmed a death rate approximately one-third of that found for the same age men on the U.S. mainland. It was further found that this low mortality and reduced severity of atherosclerosis of the coronary arteries could not be explained by out-migration of the sick, errors in the statement of age, under-reporting of deaths or significant errors of diagnosis.

Further pilot field surveys in the urban and rural populations revealed a heterogeneity of diet, physical activity and lipid levels which would make possible testing of the validity of the risk factors established for the Framingham population in another U.S. population with a very low incidence of coronary disease.

A relatively high autopsy rate of 55% of all deaths provides a further opportunity for direct correlation of severity of lesions in the coronary vessels with antecedent biochemical measurements in this population.

Methods Employed: A special census of all males age 45-64 living in specified rural and urban municipios has been conducted to identify a total population of 4,000 rural, 4,000 urban lower socioeconomic and 4,000 higher socioeconomic subjects.

A comprehensive standardized protocol was developed and pretested, a manual of operations completed and staff trained in conducting the necessary procedures for information collection, clinical, laboratory, autopsy, data processing and quality control.

A prospective epidemiological investigation on this population began in July 1965 and completed its baseline examination cycle in December 1968. An incidence examination cycle was initiated under a schedule allowing a 2 year interval from the first examination. Concurrent morbidity, mortality and autopsy data are being gathered to relate to baseline measured characteristics.

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Progress to June 1972: The second round of examinations for development of accurate incidence data was completed in September 1971 with 91% of living subjects re-examined by the standard protocol procedures. The low incidence of CHD during this 2½ year interval has confirmed the fact of reduced levels of clinical coronary disease in this population.

Completion of one further incidence cycle has been recommended by the Epidemiology and Biometry Advisory Committee following a project site visit in relation to the F.Y. 1973 continuation contract.

Data from the Exam II are being edited to prepare a clean tape for incidence analysis even with the limited number of cases available for such analysis.

Major Findings: A provisional annual incidence of myocardial infarction among men aged 45-64 has been found to be 3.7 per 1,000 in this Puerto Rican population compared with 9.4 per 1,000 found in Framingham men of the same age. This incidence of MI is 38% of the observed incidence of Framingham and is confirmatory of the associated low mortality previously observed in this population. Urban-rural differences in risk factor characteristics are rather marked and provide interest to see how these will relate to comparative incidence of MI between the urban and rural populations. The analysis of characteristics of rural vs urban men 40-69 revealed significant differences in serum glycerides, cholesterol, blood glucose, relative weight, physical activity and the dietary variables of per cent of calories from fat, and per cent of calories from starch.

No correlation of physical activity with serum cholesterol was found. However, as much as one-half of the difference in serum cholesterol and as much as two-thirds of the difference in serum glycerides could be explained on the basis of differences in relative weight, blood glucose and physical activity index. Of these variables, relative weight was the most significant determinant of both glycerides and cholesterol level. These results suggest that the principal determinants of these lipid values in the Puerto Rican population under study are factors which promote obesity rather than the specific nutrient content of the diet. These results were published in Circulation April 1972.

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Significance to Bio-medical Research and the Program of the Institute: This study in a U.S. population exhibiting low coronary disease rates provides a potential for establishing the characteristics which are natural determinants of low coronary disease rates. From the preliminary trend of findings, it appears that data will be developed to extend down to a lower range the importance of cholesterol levels and should clarify the importance of triglyceride levels which have been measured in this population.

Extensive dietary data have also been collected and will be subjected to intensive analysis to seek further clarification of this important aspect of the question.

Proposed Course of Project: Following a project site visit by members of the Epidemiology and Biometry Advisory Committee, the recommendation has been made to increase the period of incidence observation into an additional cycle to provide sufficient added events to enable the establishment of definitive conclusions relating to the major variables under investigation.

Publications:

Garcia-Palmieri, M.R., et al.: Interrelationship of serum lipids with relative weight, blood glucose and physical activity. Circ. 45: 829-836, 1972.

Serial No. NHLI- TEB
1. Clinical Applications
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Development and Evaluation of Nutrition Education Programs for Dietary Management of Hyperlipidemia

Previous Serial Number: None

Principal Investigator: Marilyn Farrand, Nutritionist, has served as Executive Secretary and Coordinator for the Review Committees and will serve as Project Officer for the contracts.

Other Investigators: Dr. Mary McCann, Columbia University; Dr. Helen Brown, Cleveland Clinic; Dr. William Insull, Rockefeller Institute; and Miss Jeanne Tillotson, NHLI, are members of the Contract Monitoring Committee.

Man Years:

Total:	0.3
Professional:	0.3
Other:	0.0

Project Description:

Objectives: The objective of these nutrition education programs is to develop, test, and evaluate promising techniques for nutrition education for practical use with hyperlipidemic patients. The immediate application of these programs is to the Multiple Risk Factor Intervention Trial. However, the results should be more broadly applicable to other patient education programs involving dietary treatment of hyperlipidemia.

On August 26, 1970, the OADCA of NHLI convened a meeting of nutritionists to identify certain practical needs of problems related to more widespread application of dietary treatment of hyperlipidemia. Six recommendations were made, and those most directly related to these projects are as follows:

1. Increase the effectiveness of patient nutrition education programs by utilizing experts in education and motivation to assist nutritionists in the development of better methods and materials for influencing both the patients' ability to learn and to accept the diet programs.

2. Devise means to evaluate the success of nutrition programs as shown by diet adherence.

3. Develop materials for professional education of nutrition personnel, such as films, slides, and taped lectures.

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4. Demonstrate to physicians the value of nutritionists providing diet counselling by establishing and encouraging model services in various community facilities such as lipid clinics, hospital nutrition clinics, health departments, and in voluntary agencies, such as Heart Associations, and evaluating the effectiveness of these services.

Based upon these recommendations, RFP NHLI 72-15 Development and Evaluation of Improved Nutrition Education Programs for Dietary Treatment of Hyperlipidemia was prepared and issued December 17, 1971. Twenty-one proposals were received and reviewed by a Technical Review Committee on March 13-14, 1972. After further review by NHLI staff and several members of the initial review committee, two contracts were recommended for funding at a total of approximately $300,000. The projects are those proposed by the Chicago Heart Association (Principal Investigators: Dr. Louise Mojonnier, Dr. David Berkson, Mrs. Yolanda Hall) and the University of Chicago (Principal Investigators: Dr. Richard Jones and Mrs. Dorothea Turner). Although both of these contracts are related to nutrition education, the populations, settings and area of emphasis are somewhat different.

The Chicago Heart Association contract is to develop a cooperative program between the Chicago Heart Association, the Chicago Board of Health, and St. Jospeh Hospital to teach hyperlipidemic participants to modify their intake of the five food groups that contribute most of the saturated fat and cholesterol to the typical American diet, using trained lay personnel for the actual teaching.

Objectives are:

1. To develop and test four educational methods -- individual, group, self-teaching and multi-methods -- in populations of different socioeconomic, ethnic and racial backgrounds, and in three types of settings: a nutrition counselling facility, a community health center and a hospital.

2. To teach diet modification as a change in habits of eating the five food groups, rather than following a diet prescription tailored to the individual.

3. To train lay personnel to become nutrition counselling aides capable of teaching hyperlipidemic participants how to modify their food intake, and of motivating them to maintain the new eating patterns until they have become habitual.

4. To develop audio-visual teaching materials suitable for use with large numbers of people with various socioeconomic, ethnic and racial patterns; these materials will include programmed self-teaching and TV sequences for use with closed-circuit TV in a hospital.

5. To evaluate the program using as measures of effectiveness self-administered questionnaires, pre-test and post-tests, comparative costs, changes in weight and serum lipid levels.

The University of Chicago contract will be conducted at the hospital outpatient nutrition clinic. Specific objectives are as follows:

1. To develop brief, self-administered questionnaires and educational techniques to provide educational diagnosis of the patient.

2. To develop a brief self-administered questionnaire to define the patients' emotional status and motivation toward health improvement.

3. To assess available audio-visual and printed materials used in diet counselling for their suitability in teaching particular types of learners.

4. To develop new programs of instructions and/or graphic materials for use in counselling for those patients whose mode of learning is not matched by present material.

5. To compare the ease, time required and success of patient education when the appropriate program is provided as compared with the control situation.

6. To correlate selected patient parameters with success of diet therapy.

Methods Employed: The Chicago Heart Association project will be carried out at three centers representing different settings for delivery of health care and serving different populations. The Heart Asssociation serves industrial and office workers; the hospital, patients from a variety of ethnic and socioeconomic backgrounds; and the health center,the inner-city black community. Persons invited into the study will be men and women, 25-59 years of age, with serum cholesterol values greater then 250 mg/dl. At each center, 150 patients will be enrolled. They will be randomly assigned to one of five groups: control, individual, group, self-teaching or multi-method. Appropriate educational materials and procedures will be developed for them as well

as for the nutrition aides.

The effectiveness of various educational methods within one health care setting and among the several settings with different populations will be tested. The teaching methods will be compared in terms of learning achieved, effect on weight and serum lipids and also by changes in food patterns. Diet adherence will be evaluated by food records and 24-hour recall; adherence measured by these means will be compared to a simplified scoring method based upon the five major food groups. Family food purchases will also be evaluated. The relationship between diet adherence and life situations will be assessed. Information collected on participants' perceptions of the amount of support from his spouse, other family members and physician will be used to supplement adherence evaluation. The relative costs of the teaching methods will be ascertained.

Participants counselled in the hospital outpatient nutrition clinic will receive initial diet education while hospitalized. Hospital menus and television programs will be used for initial learning experiences.

The second project at the University of Chicago outpatient nutrition clinic will involve about 400 hyperlipidemic patients. They will represent various educational, economic and cultural backgrounds. Their preferred learning method will be ascertained by a questionnaire designed particularly to provide an educational diagnosis. Thereafter, they will be assigned to various study groups.

For one group of patients, the teaching program will be matched to their learning category. Three other patient groups (controls) would be included: I, patients taught without benefit of an educational diagnosis; II, a small group upon whom an antithetical teaching modality is imposed; and III, a group who will receive an educational diagnosis but a standard course of diet instruction. Success of instruction will be measured by nutritionists' estimates of adherence, food records, and from the changes in body weight and serum lipids.

Significance to Biomedical Research and the Program of the Institute:
Dietary modification to reduce serum lipids is considered a vital component of treatment of hyperlipidemia, and nutrition education programs is essential for successful application of scientific advances being made. The need to provide these programs will grow as more patients with hyperlipidemia are identified. However, the effectiveness of present efforts to produce maximum, long-term adherence to diet modification needs improvement. Interdisciplinary efforts among physicians, nutritionists, behavioral scientists and educational

specialists is essential. There is a need to develop appropriate methods and materials for patients with varying educational and cultural backgrounds for use in various settings, such as voluntary agencies, hospital and health department nutrition clinics, and private physicians' offices. Concurrently a shortage of professional health personnel exists. Extension of nutrition services by improving educational methods and materials for nutrition is needed. Also, inclusion of other trained personnel in the educational programs will add to the manpower for these programs.

Both of these nutrition education projects will make significant contributions to improved nutrition education for the Multiple Risk Factor Intervention Trial, as well as many other nutrition programs sponsored by NHLI and others.

The Chicago Heart Association program involving three medical settings serving different patient groups and using various approaches to education will provide experiences that might readily and fruitfully be followed throughout the country. The plan to teach individuals to modify their intake of five food groups that contribute most of the saturated fat and cholesterol to the American diet is a realistic, simple approach to changing food habits. It is essential to have practical models for teaching large numbers of patients. Cost of delivering this type of program is low enough to have wide applicability.

The adaptibility of the educational program to various settings and populations will be demonstrated. Provision of some education while patients are hospitalized will be valuable. The community health center program will provide research into educational methods and adaptation of fat modified diets for low income groups. Diet counselling in the voluntary agency represents a resource for private physicians.

Other significant contributions are that the teaching methods and materials will be valuable for many programs, and the costs of the most effective methods will be determined to assist in future planning. Experimentation with simple ways to collect diet data and rate adherence will provide practical approaches for long-term follow-up for reinforcement, clarification and encouragement. Development of programs to train lay personnel to give nutrition guidance will greatly expand the pool of personnel necessary for the Multiple Risk Factor Intervention Trial, as well as for extending nutrition knowledge to the public at large.

The University of Chicago Project will be the first attempt to apply newer ideas from educational philosophy to a medical setting. It is hoped

that with simple objective tests it will be possible to recognize the major types of learners and also that appropriate learning experiences can be matched. Also, it may be possible to predict the motivational level of a patient by gaining some insight into his emotional state. More efficient and effective programs will result, for learners will not only be categorized but appropriate educational programs will be developed. Such a technique might be applied to other health areas. Certain aspects of the educational program might be assigned to less skilled personnel, thereby adding to the resources for patient education and care.

Proposed Course: The two contracts described are being negotiated; projects will be completed in two years. Plans are also underway to coordinate some aspects of the projects with each other, such as the development and use of educational materials. Also, the educational diagnosis questionnaire developed by the University of Chicago will be administered to patients enrolled in the Chicago Heart Association project.

Plans are to monitor these contracts by a committee composed of several members of the Technical Review Committee and selected Clinical Applications staff members. Eventually investigators associated with these projects will cooperate with nutritionists involved in the planning of the Multiple Risk Factor Intervention Trial so that maximum benefit may be derived for the latter project.

Serial No. NHLI-TEB-
1. Clinical Applications
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Nutrition Research and Consultation

Previous Serial Number: None

Principal Investigator: Marilyn Farrand, Nutritionist

Other Investigators: None

Cooperating Units: U.S. Public Health Service Hospital, Baltimore, Maryland

Man Years:

Total:	0.7
Professional:	0.7
Other:	0.0

Project Description:

During the past year, the nutritionist's work has included consultation with other Clinical Applications staff members to develop and implement plans for program activities related to nutrition. In addition, guidance has been provided to other nutrition related projects within NHLI and outside research programs and health agencies that either have nutrition research and services related to cardiovascular disease nutrition or plans to develop these activitites.

The nutritionist's participation during the past year has been in the following major areas:

1. Provided consultation concerning the nutrition component of research in the Lipid Intervention Project at Social Security Administration, Baltimore, Maryland, which is in its second year of operation. Improvements in the nutrition materials and procedures were made in collaboration with the project nutritionist. Nutrition education programs are underway for all patients as planned and will be completed by Fall 1972.

2. Provided nutrition consultation for the Controlled Clinical Trials of Therapy for Hypertension in the General Population.

3. Assisted in the preparation of the nutrition component of Request for Proposals NHLI 72-16 Multiple Risk Factor Intervention Trial, for the Prevention of Coronary Heart Disease, and NHLI 72-17 Coordinating Center for Multiple Risk Factor Intervention Trial.

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4. Provided professional staff with nutrition information for use in program development and coordination with nutrition activities in NHLI and other government agencies.

5. Identified areas for further research, resulting in the preparation and issuance of RFP NHLI 72-15 Development and Evaluation of Improved Nutrition Education Programs for Dietary Treatment of Hyperlipidemia, and organized the review process of these proposals.

6. Participated in nutrition programs sponsored by voluntary and official health agencies for patient and professional education related to nutrition in cardiovascular disease (Chicago Heart Association, Mid-Hudson Dietetic Association, Tri-State Dietetic Association).

7. As a member of the American Heart Association's Nutrition Committee's Subcommittee of Dietitians and Nutritionists, assisted in the development of educational materials and programs for patients and professional personnel. Serves as co-editor of the Association's publication NUTRAH - Nutrition Programming in the Community.

8. Provided diet consultation for four hours weekly for patients at the PHS Outpatient Clinic in Washington, D.C.

Publications:

Farrand, M.: Book Review of "The Low-Fat, Low Cholesterol Diet" by Bond, C. B., Dobbin, E. V., Gofman, H., Jones, H. C., and Lyons, L. J. Am. Dietet. A. 59: 498, 1971.

Farrand, M.: Book Review of "Sugar - Chemical, Biological and Nutritional Aspects of Sucrose" by Yudkin, J., Edelman, J., Hough, L. J. Am. Dietet. A. 60: 409, 1971.

Serial No.
1. Clinical Applications, NHLI
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Activities in Conjunction With New NHLI Initiatives Involving Nutrition-Related Interest

Previous Serial Number: None

Principal Investigator: Jeanne Tillotson, Consultant Dietitian

Other Investigator: Miss Marilyn Farrand is working in the nutrition education phase.

Cooperating Units: This is a developing area; liaison has been established with other NHLI programs on an informal basis.

Man Years:

Total:	1.5
Professional:	1.0
Other:	0.5

Project Description:

Objectives: To make expertise and methodologies from epidemiologic research available to nutrition programs being developed to fit the needs of the new SCOR, LRC, and MRFIT programs. In addition, considerable staff time has been devoted to documenting the unsolved problems in applied cardiovascular nutrition as the needs in this area become more obvious.

Methods Employed: As new objectives develop, there is increasing opportunity for consultation with those directly responsible for dietary data collection in the new NHLI projects. Our role is one of providing assistance when requested, particularly sharing experience and written material with newly-appointed project dietitians.

Considerable preliminary work has also been done in pinpointing areas of cardiovascular nutrition which may benefit from increased NHLI attention. focusing increased NHLI attention on items such as the following:

1. Consideration of the need for a NHLI approved national diet-heart policy statement.
2. Consideration of national diet-heart policies as they relate to children and adolescence.
3. Development of behavioral methods for dietary counseling to influence lifetime eating habits effectively.
4. Guidance and persuasion to improve food labeling laws in accordance

with diet-heart principles.

5. Exploration of problems related to lack of up-to-date composition figures for those working in cardiovascular nutrition today.

All of these activities are in the formative stage pending formal programming direction and guidance.

Serial No.
1. Clinical Applications, NHLI
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Nutritional Studies in Conjunction With Epidemiological Studies of CHD Conducted by the Branch.

Previous Serial Number: None

Principal Investigator: Jeanne Tillotson, Consultant Dietitian

Other Investigators: None

Cooperating Units: Programa de Salud Del Corazon, University of Puerto Rico, San Juan, Puerto Rico
Tripartite Study:
Honolulu Heart Program, Honolulu, Hawaii
Atomic Bomb Casualty Commission, Hiroshima, Japan
California Japanese-American Stroke Study, University of California, Berkeley, California
Framingham Heart Program, Framingham, Massachusetts

Man Years:

Total:	1.5
Professional:	1.0
Other:	0.5

Project Description:

Objectives: The nutritional studies in the above areas were designed to assess the relationship of dietary habits to serum lipid levels, and to the prevalence and incidence of CHD. These particular geographic locations are of interest because the usual dietary patterns of Puerto Ricans and of the Japanese of Japan and Hawaii are sufficiently different from mainland-USA dietary patterns to make possible an interesting natural experiment. Dietary studies were conducted using comparable methods in Framingham, Massachusetts and in a Japanese-American population in the San Francisco Bay area in order to obtain suitable dietary data on mainland-USA groups for comparison purposes.

Methods Employed: Dietary interviewing, coding and computation methods have been designed to be comparable in the Puerto Rico, Hiroshima, Honolulu, San Francisco, and Framingham studies in the initial interview phases. Subsequent dietary substudies in Puerto Rico, Hiroshima, and Honolulu were designed to give more detailed dietary information using methods suitable for the particular populations under study, taking into consideration such items as literacy levels and subject time available. Interviewing has now been

completed in all except the Puerto Rico study, and statistical analysis is proceeding using standard correlation and regression techniques.

Major Findings: Preliminary analysis of data from the tripartite study of men of Japanese ancestry in Japan, Hawaii, and California has been completed and the publication is in the second-draft stage. Serum cholesterol levels show significant positive regression with per cent calories from saturated fat and significant negative regression with per cent calories from carbohydrate within each of the three cohorts studied. The paper in preparation will also discuss interesting relationship between serum lipid levels and nutrient intake by levels of relative weight; relative importance of simple and complex carbohydrate intake; et cetera. The results of the study of rural and urban Puerto Ricans are still under statistical investigation, but probaby will be similar. The data collected in a comparable manner during the last two years of the Framingham study will be used principally for comparison purposes, since it appears to be almost impossible to discern a relationship between diet and serum lipid levels in populations where high-calorie, high-fat intakes have been customary over an entire lifetime.

Significance to Biomedical Research: While it has been demonstrated in clinical studies that alteration of kind and amount of fat in the diet will affect serum cholesterol levels, and while past epidemiologic studies have demonstrated significant correlation between serum cholesterol levels and intake of saturated fat between groups, rarely if ever has this been demonstrated within free-living groups studied. In the tripartite study of Japanese men, these within-group relationships are statistically significant but at the same time do not explain more than a small per cent of the variation in serum cholesterol levels seen, pointing to the importance of other as yet unexplained factors. However, the findings demonstrate that serum lipid levels in free-living groups can be affected by dietary intake, and indicate the public health importance of these relatively small, non-hazardous changes which should be encouraged in the national diet pattern.

Significance to the Program of the Institute: An unexpected bonus of these dietary studies is the development of methodology applicable to newly-developing programs of the Institute. Practical experience has been accumulated using the four principal dietary interview methods; in developing food composition tables and programs for dietary data processing; in formulating coding rules; and in application of epidemiologic principles to dietary data collection. This experience is now useful in the newly-developing interests of the SCOR, LRC, and MRFIT programs. While no one method can be applied directly to all projects because of their diverse objectives and populations,

the experience gained provides a wealth of practical information on advantages and disadvantages of each, and should make it possible to make wiser administrative decisions on the basis of past experience.

Proposed Course: Tripartite Study of Japanese Men -- Analysis based on data from all three sites is now under way. More detailed dietary data (using more intensive dietary interview methods and more detailed food composition tables) is ready for within-cohort analysis in the Honolulu Heart Study. Food samples were collected from the three areas and have been analyzed for fatty acid content; analysis for dietary cholesterol is in progress. Puerto Rico Study -- Analysis of data from the first examination cycle is in progress; the more detailed dietary data from Exam II has not been completely processed yet, but should be available for analysis during the next fiscal year.

Dietary data from both major research projects should become more valuable as CHD incidence data accumulate.

Serial No.
1. Respiratory Disease
2. Clinical Applications
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Coordination of Cardio-Respiratory Research

Previous Serial Number: None

Principal Investigator: Albert Roberts, M.D.

Other Investigators: None

Man Years:

Total:	1.9
Professional:	1.4
Other:	.5

Project Description:

Objectives: To investigate the prevalence, incidence, and etiologic and risk factors in respiratory disease--in particular, but not exclusively, obstructive respiratory disease--through analyses of data produced by collaborative studies of heart disease of the Clinical Applications Program, and through development of new investigations in the pulmonary field.

Methods Employed: The data generated by these collaborative studies are reduced to a common format and subjects classified according to pulmonary function tests results (after Gaensler-Wright standards for pulmonary impairment). This yields three main categories: a. "Positive" (moderate and severe obstructive impairment), b. "Borderline" (mildly obstructive) and c. "Negative." Further subdivided into degrees of severity the three categories are then correlated, by age groups, to medical and environmental parameters with known or assumed bearing on lung disease. The standardized methodology applied to these studies permits individual analysis of every population group and their direct comparison to each other.

Special emphasis continued to be given this year to exploring the relationship of genetic serum α_1-antitrypsin (AAT) deficiency and obstructive pulmonary disease, particularly pulmonary emphysema. Further insights into the nature of genetic AAT deficiency led to the conclusion that such defect can only be ascertained by means of phenotyping techniques which have become more generally available during the past year. This called for development of the necessary skills in those laboratories associated with our studies where the subject of AAT deficiency is being investigated, namely Yugoslavia and Honolulu.

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1. Respiratory Disease
2. Clinical Applications
3. Bethesda, Maryland

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Individual Project Report
July 1, 1971 through June 30, 1972

As a counterpart for these more discriminating serum analyses, the need for an acceptable identification of the presence or absence of pulmonary emphysema among study subjects became apparent. Both in Yugoslavia and Honolulu, pulmonary physiology laboratories had to be updated in order to perform lung mechanics and gas transfer measurements necessary for this purpose.

Attempts to extend these approaches at other sites, especially Puerto Rico, were less successful due to scarcity of resources.

Major Findings: 1. Respiratory data collected during the First Examination (1964-66) of the Cardiovascular Disease study in Yugoslavia were further analyzed. This showed that the high prevalence of airway obstruction among the different groups (Remetinec: urban 39%, rural 53%; Tuzla: urban 49%, rural 33%) correlated well with other parameters such as clinically diagnosed chronic bronchitis; productive chronic cough; occupation; smoking habits, etc. But no clues were detected to explain the unexpected reversal of urban-rural ratios between the two areas. The reversal held up for age and smoking categories and the possibility that genetic factors may be implicated in those differences is now being explored by the new Respiratory Disease project initiated under PL-480 support in the Fall of 1971.

2. The Second Examination (1968-70) of 7000 Japanese subjects in the Honolulu Heart Study revealed that the prevalence of airway obstruction among that cohort was 15%, subdivided into 4% "positives" (moderate or severe obstruction) and 11% "borderlines" (mild obstruction). Against this rather "low" prevalence of obstructive pulmonary impairment (by comparison to other mainland groups) stood the previously reported finding of a very high proportion of subjects with low serum antiprotease activity. Because the method on which this finding was based, i.e.: direct determination of the trypsin inhibitory capacity of serum, is subject to question, a new investigation of this genetic defect was initiated recently including the measurement of AAT content in individual sera and its further characterization by phenotyping. This new study now underway will also investigate the presence of emphysema among AAT deficient subjects, and also the possible relationship of liver disease to AAT contents.

Significance to Bio-Medical Research and the Program of the Institute: The need for investigations to establish the prevalence and incidence of obstructive respiratory disease and their variation according to ethnic factors and environmental influences has been repeatedly recommended by every pulmonary advisory group. The collaborative studies of the Clinical Application

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3. Bethesda, Maryland

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Program, involving large populations of different stock and background on which extensive correlative data have been collected over the years, offer unique opportunity for such investigations. These well identified population groups are of particular usefulness for the newer studies of genetic factors associated with lung disease, and this is in accordance with the Institute Lung Program's priorities in this field.

Proposed Course: 1. The "Investigation of Etiologic and Risk Factors in Respiratory Disease Among Yugoslavian Populations" supported by PL-480 funds is now in the first of a planned 3 years of operation. This study involves close collaboration between Yugoslav investigators and NHLI staff. It is planned that at the end of the first year key investigators from both countries will review initial findings and introduce any necessary refinements in the study protocol to enhance its scientific yield. A technological manual is now being prepared for publication and is targetted for release in the Summer of 1972.

2. The Honolulu respiratory disease study will be pursued as planned. Data collection is now underway as part of the 3rd Cardiovascular Examination. The facilities for phenotyping sera developed in connection with this project are first in the area and their progressive enlargement will make them a unique resource for such studies in the Pacific. These will also be used for future investigations sponsored by NHLI. Equally new to this area is the new facility for measuring Lung Compliance and Elastic Lung recoil at the Queens Medical Center, Honolulu, as a result of this project.

3. Puerto Rico: A proposed "pilot" study of 100 selected cases with demonstrable airway obstruction from which sera are available was agreed to in principle early in 1972. Implementation is pending the decision to proceed by Puerto Rican investigators.

Publications:

Kozarevic, D., Roberts, A. and Pirc, B., "Prevalence of Chronic Obstructive Lung Diseases Among Rural and Urban Populations in Two Different Areas of Yugoslavia." In Press. (Will appear in a Monograph based on the Seminar on Ecology of Chronic Non-Specific Respiratory Diseases held in Warsaw, Poland, September 1971. Official Polish Publication.)

Serial No. NHLI-CA-2
1. Associate Director for Clinical Applications
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971 through June 30, 1972

Project Title: Medical Liaison with the Coronary Drug Project

Previous Serial Number: NHI-EB-2

Principal Investigator: Dr. Michael J. Davidson, Office of the Associate Director for Clinical Applications, NHLI, served as Medical Liaison Officer for the Coronary Drug Project.

Note: This refers only to services provided by the Office of Associate Director for Clinical Applications. The study itself is being conducted by grantees, including Dr. Robert W. Wilkins, Chairman of the Policy Board; Dr. Jeremiah Stamler, Chairman of the Steering Committee; Dr. Christian R. Klimt, Director for the Coordinating Center; and clinician-investigators in 53 participating grantee institutions.

Other Investigators: Dr. William J. Vicic, Epidemiology Branch, NHLI, served as Assistant Medical Liaison Officer for the Coronary Drug Project.

Cooperating Units: 1) Molecular Disease Branch, NHLI (Dr. Robert I. Levy) for pharmacological consultation;

2) Laboratory of Chemical Pharmacology, NHLI (Dr. James R. Gillette) for pharmacological consultations;

3) Biometrics Research Branch, NHLI (Dr. Max Halperin, Dr. William Friedewald and Mr. Fred Ederer) for statistical liaison;

4) Therapeutic Evaluation Branch, NHLI (Dr. Eleanor M. K. Darby) for grants management aspects;

5) Central Laboratory, National Communicable Disease Center, U.S. Public Health Service (Dr. Gerald Cooper, Dr. Alan Mather, and Dr. Adrian Hainline) for

performance of biochemical blood and urine studies of study patients;

6) Drug Distribution Center, USPHS Supply Service Center (Mr. Salvatore Gasdia) for the procurement and distribution of study drugs;

7) Heart Information Center, NHLI (Mr. William E. Sanders and Miss Sandra L. Kamisar) for assistance in developing study publicity.

Man Years:

Total:	2.0
Professional:	1.5
Other:	0.5

Project Description:

Objectives: The Medical Liaison Officer is the representative of the Clinical Applications Program to the Coronary Drug Project. He serves as the chief medical link between this grant-support study and the National Heart and Lung Institute. His function is to assure that full cooperation and communication exists between this study and the administration of the National Heart and Lung Institute.

The Medical Liaison Officer serves as recording and executive secretary for the Policy Board and Steering Committee of this study. In addition, he is a member of the Data and Safety Monitoring Committee, Hepatology Committee, Laboratory Committee, Criteria Committee, Editorial Review Committee, Natural History Committee, Mortality Classification Committee and CDP Resource Committee.

He is also responsible for working with the Coordinating Center at the University of Maryland, Baltimore, Maryland; with the Central Laboratory at the National Communicable Disease Center, Atlanta, Georgia; and with the USPHS Supply Service Center at Perry Point, Maryland.

The principal objectives of this study are as follows: 1) To determine the ability of four lipid-altering drugs to reduce mortality and recurrences from myocardial infarction among men who have already experienced one or

more proven myocardial infarctions. 2) To determine whether the degree to which these drugs change serum lipids is correlated with any effect on mortality and morbidity rates. 3) By studying the control group as intensively as the treatment groups, to gain further information on the long-term prognosis of myocardial infarction. 4) To acquire experience and knowledge concerning the techniques and methodology of long-term clinical trials.

Methods Employed: The project is a cooperative clinical trial involving random and double-blind assignment of patients to one of six drug regimens. The patients will be men aged 30 to 64 years who have survived one or more myocardial infarctions. After allocation to treatment, patients will be followed at the participating clinics for five years or until death. It is estimated that in order to establish unequivocally a 25 percent relative reduction in five-year mortality rate approximately 8400 patients will be required.

Major Findings: On the basis of recent findings from the Coronary Drug Project, certain protocol changes are being made in this therapeutic trial being conducted under the auspices of the National Heart and Lung Institute. These changes resulted from the latest review of findings by the Data and Safety Monitoring Committee and the Policy Board.

The Data and Safety Monitoring Committee, composed of selected study personnel and outside consultants, on a regular basis carefully analyzes on-going results for both beneficial and potentially adverse effects. On the basis of the latest complete data, representing an average follow-up of 36 months, recommendations for protocol changes were made by this group, and adopted by the Policy Board of the study. These data and resultant recommendations were also received and affirmed by the Steering Committee and Technical Group. These protocol changes involved patients receiving one of the study regimens.

All patients receiving the dextrothyroxine preparation are being removed from this regimen. This group of patients, numbering 1,110 men at entry, will continue to be followed with regular visits according to the study protocol. This action has been recommended because the latest data indicate an unfavorable trend in a subgroup of patients on this medication. Also with this regimen, no overall trend toward a beneficial effect in reducing mortality was discerned to outweigh the apparent adverse effects. Furthermore, no subgroup with a sustained favorable trend could clearly be identified.

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These decisions indicate the concern of the Coronary Drug Project to minimize any possibility of subjecting study patients to potential harm. The quantitative documentation leading to these decisions is to be published in a medical journal as soon as possible. All data from the study are continuing to be reviewed for adverse as well as beneficial effects.

Significance to Bio-Medical Research and the Program of the Institute: The Coronary Drug Project has been developed to meet a specific need in the field of atherosclerosis research. Drugs are available which effectively reduce the concentration of blood cholesterol and other lipids. Although elevated levels of these blood lipids are closely associated with the occurrence of coronary heart disease, proof is lacking that active intervention to reduce the levels of cholesterol and other blood lipids will improve the survival rate of men who have coronary heart disease. The demonstration of such an effect would have significance, both for atherosclerosis research and for the therapy of coronary heart disease.

Proposed Course: Following enrollment into the study, each patient will be followed for a period of five years.

Publications:

Coronary Drug Project Research Group: The Coronary Drug Project. Findings leading to further modifications of its protocol with respect to dextrothyroxine. J.A.M.A., 220:996-1008, 1972.

Serial No. NHLI-TEB-HP2
1. Associate Director for Clinical Applications
2. Therapeutics Evaluation Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1971, through June 30, 1972

Project Title: Controlled Clinical Trials of Therapy for Hypertension in The General Population - NHLI Hypertension Detection and Follow-Up Program

Previous Serial Number: NHLI-TEB-HP1

Principal Investigator: Dr. Gerald H. Payne, Epidemiologist, Therapeutics Evaluation Branch, Office of the Associate Director for Clinical Applications, served as Executive Secretary for the review panels, NHLI coordinator for the Program and is serving as Project Officer for the related contracts. He is a representative of NHLI on the Steering Committee.

Other Investigators: Dr. Max Halperin, Chief, Biometrics Research Branch, is serving as the chief NHLI Statistical Consultant for this project and is a voting member of the Steering Committee of this collaborative trial.

Dr. Thomas Hoffman is assistant to the Project Officer. He serves as liaison officer and recording secretary for the Steering Committee.

Cooperating Units: Consultation provided by Dr. Gerald Cooper, Chief, Clinical Chemistry and Hematology Branch, CDC, Atlanta.

Man Years:

Total:	3.0
Professional:	2.0
Other:	1.0

Project Description:

Introduction: The Principal Investigators and Co-Investigators of the nine clinical centers and the Coordinating Center have met together four times as a Steering Committee and in numerous subcommittees on several other occasions to develop plans and a protocol for the Phase II cooperative Hypertension Detection and Follow-Up Program. Each of the investigators has carried out pilot studies within his own community.

A Policy Advisory Board was appointed by the Director of NHLI in September. They first met November 25 to review a Protocol Draft for Phase II and approved the recommendation that up to six new centers be sought to

assure an adequate source for 10,500 hypertensive patients for the cooperative Phase II part of the program which will utilize a common Protocol.

RFP-NHLI-72-14, "Additional Clinical Centers for the NHLI Hypertension Detection and Follow-Up Program in Representative General Populations", was released December 17, 1971, after an announcement in the Commerce Business Daily.

Fifteen proposals were received and reviewed by the Technical Review Committee on March 9-10, 1972. Five additional centers were approved and recommended for funding. Negotiations are in process.

On April 29, the Policy Advisory Board reviewed the revision of the Protocol and recommended approval for launching Phase II. They also reviewed and approved the progress reports and requests for contract renewal from the nine clinical centers and one coordinating center already participating.

Objectives: The purpose of the Hypertension Detection and Follow-Up Program is to determine the efficacy of antihypertensive therapy in the whole spectrum of those with elevated blood pressure in community-based populations, including women, younger adults, and many with no target organ disease but with persistent elevation of blood pressure on two or three occasions of casual determinations. Exclusions will be held to a minimum and a great effort will be made to motivate the kinds of persons eliminated from other trials as non-compliers to be participants in this Program.

Methodology: It is proposed that individuals age 30-69 with elevated blood pressure in the defined community be identified principally through primary screening in homes. A 50% random sample of those identified and confirmed at follow-up screening clinics to have elevated diastolic blood pressure $\geq$95 mm Hg will be invited to participate in the Stepped Care Group. They will receive energetic care by the Program staff. "Stepped Care" refers to the plan of therapy in which mild antihypertensive agents will be initially prescribed and more potent agents added, if necessary, in a stepwise manner until the goal blood pressure, <90 mm Hg diastolic, or as close to goal pressure as tolerated, is reached. It is recognized and anticipated that a certain number of moderately and severely hypertensive individuals cannot be brought down to goal levels. The other 50% sample will be in the Regular Care Group who will be referred to the usual sources of care in the community.

The primary end point is total mortality measured by annual surveillance, and the principal aim is to determine whether a significant reduction in total mortality can be effected in the Stepped Care Group of hypertensives in comparison to the Regular Care Group. It is anticipated that a total of 10,500 hypertensive individuals divided randomly into the two groups and followed for five years will be adequate for the purpose of this Program.

A secondary aim will be to assess the effects of the Stepped Care Program on secondary and intermediate end points such as cause specific mortality, non-fatal myocardial infarction, stroke, congestive heart

failure, progressive hypertension, ECG abnormalities, cardiac enlargement as measured by increase in heart size on chest x-ray, renal failure (as measured by elevated serum creatinine). The above indices and other co-morbid factors will be determined in the hypertensive individuals at base-line and at annual and/or biennial examinations. Evidence of a reduced level or disappearance of certain of the above abnormalities when observed at base-line will also be evaluated, e.g. elevated blood pressure, abnormal heart size and LVH. Subgroup hypotheses using accumulated secondary and inter-mediate end points will be tested.

Total mortality in the entire population screened will be monitored to assess the effect of treating the hypertensive strata on the population screened.

Side effects and toxic manifestations will be monitored. Factors affecting participation will be evaluated.

Special diagnostic studies in a clinically suspect subset for occurrence of secondary renal-adrenal hypertension will be carried out.

The Stepped Care Group will have intensive care and follow-up of their hypertension by Program staff at two-week to two-month intervals (or more frequently if clinically indicated). At the end of years 2, 4 and 5, the Stepped Care and Regular Care Groups will be re-examined in the Clinic for detection of secondary and intermediate end point events.

Side effects and toxicity will be monitored and necessary corrective measures will be taken according to procedures in the Manual of Operations. If these untoward events become too frequent in a specified portion of the Stepped Care Group, necessary action to modify the Protocol as may be recommended by the Data and Safety Monitoring Committee and approved by the Steering Committee and Policy Advisory Board will be undertaken.

Results: At one center a screening program primarily among blacks in supermarkets near a General Hospital detected a prevalence of 28% over age 35 and 24% over age 25 with diastolic blood pressure levels $\geq$90 mm Hg. Hypertension was confirmed at two subsequent clinic visits. Eighty-three percent of the 98 patients allocated to the "Stepped Care" group continued follow-up visits for six months. Those allocated to Regular Care were sent to the General Medical Clinic; one group (81 patients) with phone calls to remind them of appointments and the other (105 patients) without such calls. Only 33% of the former and 17% of the latter had returned for follow-up visits. After six months, an average of 58% of all the patients allocated to "Stepped Care" (70% of those continuing under care) have become normo-tensive; only 9% have shown no reduction or a rise in diastolic.

At a second center, 361 patients were identified as hypertensive ($\geq$95) of which 40.7% had no previous knowledge of hypertension. The prevalence at home screening in age group 30-69 of diastolic $\geq$95 was 41.7%.

At a third center in a home screening pilot study among middle-class whites, 84 patients were identified as hypertensive ($\geq$90) of which 26% had no

previous knowledge of hypertension. The prevalence at home screening of diastolic ≥90 in those age 30-69 was 24%.

Approximately 50% of identified hypertensives had no previous knowledge of their hypertension among primarily a blue-collar Italian-American community. The prevalence of diastolic (K4) ≥95 in home screening age 30-69 was 10.5%.

Primary home screening in a representative sample of households in a southern city yielded a prevalence of 37.5% with diastolic ≥90 mm Hg in age group 30-69. In a rural area near another southern city, a prevalence of 24% with diastolic ≥90 or 14.5% ≥95 was found.

In a large nothern industrial city, 13.6% of employees in two industries had diastolic pressure ≥95 at primary screening.

And in a western city, 17.6% of those age 30-69 going to a neighborhood health center (medically indigent) for initial health screening examinations or screened at home had a diastolic ≥95.

In a rural southern county, a cohort of obese (>50% ideal body weight) hypertensives (≥95 mm Hg diastolic) are being followed in a Phase I program. Sixty-three were randomized to a treatment group and 64 to a control (usual care) group. All patients had previous knowledge of their hypertension from a prior study. Therapy in the treatment groups is basically dietary in nature with some patients requring supplemental drug therapy if blood pressure is not controlled by diet. After four-months follow-up, it was noted that 54% of the treatment group had normotension (<90 mm Hg diastolic) pressures versus 21% of controls.

Significance to Biomedical Research and the Program of the Institute: Hypertension, as one of the major risk factors in coronary heart disease and congestive heart failure and the major risk factor in cerebrovascular disease, and hypertensive heart disease is associated with a most significant number of deaths and severe morbid events in this country. Data from the Veterans Administration Cooperative Study of the Hypertensions have demonstrated in a selected population that reduction in morbidity and mortality can be attained by treating men with diastolic blood pressure equal to or greater than 105 mm Hg. Similar trends occurred for those with diastolic blood pressures between 90 and 104. Results and current trends from other studies in selected subjects support these findings. It is not known, however, to what extent these data can be extrapolated to a general population including women and younger persons with repeated casual diastolic blood pressure levels over 95. Can these free living asymptomatic hypertensives be persuaded to maintain adequate therapy?

Several surveys -- Baldwin County in rural Georgia, 1962; National Health Examination Survey, 1960-62; and Alameda County, California, 1966 -- have found many hypertensive individuals, many of whom did not know they had high blood pressure or were not currently on adequate therapy.

NHLI has a categorical mandate for clinical trials such as this; and a responsibility to bring to the community effectively the benefits of scientific research. It is particularly important that any recommendation of therapy which may relate to millions of persons with elevated blood pressure be carefully evaluated for efficacy, toxicity and acceptibility and programmed with efficiency.

Projected Course: It is anticipated the second phase of the Hypertension Detection and Follow-Up Program will take approximately six years. After the testing and approval of the Manual of Operations and the Phase II cooperative effort by a Technical Review Panel, screening and intake of patients will begin in November 1972.

The principal investigators of the ten renewal contract proposals and five new proposals submitted for negotiations in FY72 and early FY73 totaling approximately $6.0 million are the following:

Clinical Renewal Contract Proposals

Dr. Virginia Beamer
Assistant Professor of Medicine
University of Utah
Salt Lake City, Utah

Dr. George Entwisle
Dr. Maureen Henderson
Professors of Preventive Medicine
University of Maryland
Baltimore, Maryland

Dr. Frank Finnerty
Professor (Clinical) of Medicine
Georgetown University
Washington, D. C.

Dr. Curtis Hames, Health Officer
Evans County Health Department
Claxton, Georgia

Dr. Edward Kass, Director
Channing Laboratory
Boston City Hospital
Boston, Massachusetts

Dr. Herbert Langford
Professor of Medicine
University of Mississippi
Jackson, Mississippi

Dr. Morton Maxwell, Chairman
Nephrology & Hypertension Service
Cedars-Sinai Medical Center
Los Angeles, California

Dr. Harold Schnaper
Chairman, Department of Medicine
University of Alabama
Birmingham, Alabama

Dr. Jeremiah Stamler
Professor and Chairman
Department of Community Medicine
Northwestern University
Chicago, Illinois

Coordinating Center Renewal Proposal

Dr. Richard Remington
Associate Dean and Professor of Biometry
University of Texas School of Public Health
Houston, Texas

Consultations:

1) Philadelphia Geriatric Center
Philadelphia, Pennsylvania

Consultation on research needs and community programming needs in the field of hypertension.

2) Veterans Administration Hospitals
Meetings held in Bethesda

Planning meetings with the Veterans Administration on borderline hypertension placebo trial

New Clinical Proposals

Dr. M. Donald Blaufox
Department of Medicine - Radiology
Albert Einstein College of Medicine
Yeshiva University
Bronx, New York

Dr. Nemat O. Borhani
Professor and Chairman
Department of Community Health
University of California
Davis, California

Dr. Charles A. Gilbert
Associate Professor of Medicine
Grady Memorial Hospital
Emory University
Atlanta, Georgia

Dr. Sandra A. Daugherty
Assistant Professor of Medicine
Michigan State University
East Lansing, Michigan

Dr. Reuben Berman
Mt. Sinai Hospital
Minneapolis, Minnesota

NATIONAL HEART AND LUNG INSTITUTE
Annual Report
July 1, 1971 - June 30, 1972

EXTRAMURAL RESEARCH AND TRAINING

The National Heart and Lung Institute administers cardiovascular and pulmonary research and training grant programs of great scope and diversity. Research projects supported range from epidemiological studies of large human population groups to studies of individual cells and cellular components and the biochemical reactions that occur within them. The diversity of this research is dictated by the complexity of the problems posed by the diseases involved.

In FY 1972, Institute funds totaling approximately $162 million will support grants and awards for cardiovascular and pulmonary research and training activities in colleges, universities, medical schools, public and private hospitals, public and private research foundations, and to individuals engaged in biomedical research. About 1,539 research grants will be supported at a level of almost $121 million this year. Forty-two grants, totaling $20.6 million, for specialized centers of research will be initiated. Approximately $25.9 million will be devoted to training activities; $18.7 million to support approximately 385 graduate and undergraduate training grants and $7.3 million to support 485 research fellows and career development awardees.

PROGRAM REPORTS

A description of National Heart and Lung Institute grant and award programs is presented on the following pages and is arranged according to two major subdivisions:

(1) Research encompassing six major disease areas toward which program activities are directed and which represent organizational alignment.

(2) Training including graduate research and clinical training and undergraduate training grants; postdoctoral and special fellowships; career development awards; and pulmonary academic awards.

It should be noted that the data concerning research grants--and particularly the distribution of NHLI grant funds--is based upon the total grant program which includes the Therapeutic Evaluations Branch, of the Clinical Applications Division.

ARTERIOSCLEROTIC DISEASE BRANCH

The subject matter assigned to the Arteriosclerotic Disease Branch, ERT/NHLI includes research on the etiology and pathogenesis, prevention, diagnosis and treatment of arteriosclerosis, coronary artery disease, peripheral vascular disease, cerebrovascular disease, disorders of vascular connective tissues and ageing reflected in cardiovascular disease.

Table I indicates the number of grants by category and their dollar value as supported during FY '72. The final two columns detail whether there was an increase in dollar value from FY '71.

TABLE I

	Number*	% NHLI	Funds	% NHLI	Change Number	Change Dollars
Arteriosclerotic Diseases	261	17.	$24,660,329	20.	-20	6,362,429
Arterio-sclerosis	146	10.	15,011,689	12.	-33	2,534.689
Cerebro-vascular Dis.	11	.8	409,504	.3	-20	809,319
Coronary Heart Dis.	69	4.	6,861,258	5.	13	2,314,310
Peripheral Vascular Dis.	30	2.	1,427,943	1.	20	704,111
Other	5	.3	355,935	.4	--	--

*Total NHLI grants are 1539 ($121,256,822).

The table emphasizes once again the regrettably small amount of research in peripheral vascular disease of both arterial and venous kinds. This is unfortunate since recent advances in diagnostic technology and in basic understanding of atherogenesis through lipid and coagulation abnormalities make this relatively accessible vascular bed particularly appropriate for investigation both in its own right and in relation to atherosclerosis in general.

This past year has seen the initiation of 13 Specialized Centers of Research in Arteriosclerosis. These Centers encompass an appreciable amount of research of the general grant project type. However, they have proven

to be innovative in several distinct ways and it is our view that these activities would not have developed now in the absence of the SCOR concept. The Centers have thrust into activity three major gap areas in arteriosclerosis research, e.g. pediatrics, behavior and diagnostic instrumentation.

In the pediatric area three major studies are underway. Their goal is to obtain some point prevalence data, but more particularly to obtain birth to maturity longtitudinal data in five year overlapping sets about blood cholesterol and blood pressure. These in turn will be assessed in terms of growth and development. Kindred and familial genetics of these measures will be assessed--and not merely the identification of a single abnormal kin. The significance of such adult risk factors for the child can be assessed but the ultimate meaning for him when he is grown cannot. To approach this question within a reasonable time horizon, the association of these risks in childhood will be related to the occurrance of premature vascular disease in his adult kindred. It is of interest that both ends of this question are under study; i.e. in perinatal studies children born of parents with risk-factors are being observed and from the coronary care unit children of patients with premature myocardial infarction will be traced and studied. The total number of children in the catchments is more than 20,000. The number who will come under closer and sequential study may be about 8,000.

These studies will establish some new norms for growth and development in blacks, latins, and whites, as well as data on lipids and hypertension, and will go far towards answering the question, "Is arteriosclerosis a pediatric disease." No diet or drug interventions are planned at present beyond the requirements of usual therapy.

A second area of innovation has been in behavioral research with particular emphasis on health consciousness and compliance with medical advice and therapy. Arteriosclerotic disease is chronic and subclinical for long periods. The riskfactors for it often involve lifelong habits of smoking, diet, physical activity or asymptomatic hypertension in an individual who generally regards himself as healthy, or at most, only remotely threatened. While there have been a variety of such behavioral studies a systematic investigation in relation to arteriosclerosis and its risk factors has not been made. It is known that, at present, motivation is low and compliance is poor.

A study has been mounted in three discrete communities each of about 10,000 inhabitants. Access to the media including television is available. One town will serve as a control subjected to observation only. The other two towns will be variously exposed to media messages and personal contact in relation to heart disease and health. It is hoped to measure the impact of these on health motivation and on compliance with advice and therapy. A variety of assessments of metabolic and behavioral modification will be made. A firm assessment of the value (or lack of it) of this media approach should emerge and the boundaries of the "compliance problem" will be more closely defined than at present.

In a second study the behavioral model implies influencing one person through another--in this case a child through its parent. It is a model not previously field tested. In a trial preliminary to a study in relation to diet compliance was studied over ten days with penicillin therapy for otitis media. The conceptual model was, in fact, followed but it is also noted that only one-half of the children were adhering to therapy on the fifth day of a proposed ten-day treatment. The studies will be extended to dietary adherence shortly.

In a third area of emphasis three Centers have enlisted the aid of sophisticated engineering laboratories to develop better invasive and non-invasive instruments to diagnose and characterize atherosclerotic plaques. These associations are with personnel of the Draper Laboratory (M.I.T.), the Applied Physics Laboratory (Johns Hopkins) and the Jet Propulsion Laboratory (NASA - University of California). Pulse wave analysis, phonoangiography, sonic reflectometry, hemodynamic modeling and angiographic image enhancement are under investigation. The latter in the hands of the J.P.L. now provides image enhancement that apparently exceeds the reproducibility of the angiogram itself. This Center is now attacking the latter problem. The image enhancement method is of considerable sensitivity and can read angiograms with great reproducibility.

Among a variety of basic and applied findings that have emerged from the Centers are the following: The left ventricular cardiac function of atheriosclerotic monkeys is depressed. Jogging does not influence dietary atherogenesis in monkeys. The enzyme LCAT responsible for the esterification of cholesterol has been isolated in pure form and can now be studied in detail.

Preliminary data suggest that in hyperlipoproteinemia Type II blood platelets are excessively sensitive to both aggregation and release stimulation. While the data are too preliminary to depend upon, it is interesting to speculate that recent results from Europe and the U.S.A. which suggest that clofibrate decreases the risk of heart attack independently of its lipid lowering effect may find their explanation in the platelet inhibitory action of the drug.

A last item to note about the Centers at this time is that they have been encouraged to enter into informal information exchange and they have, in fact done this with a considerable degree of freedom, and in our view, a valuable saltation in collaborative efforts and in prompt reaction to new information has occurred.

CARDIAC DISEASES BRANCH. Grants assigned to the Cardiac Diseases Branch are subdivided into five research areas whose organization into a single program is not determined by logical or by disciplinary relationships but rather by the necessity of providing a structure for their administration. Of the five, four have central disease-related themes. Two of these are largely devoted to those themes: cardiac diseases, and cogenital and rheumatic heart disease; and the other two contain, in addition, a number of grants to support research, as well as those to provide an understanding of cardiovascular pathology, arrhythmias,and heart failure and shock.

The fifth research area, cardiovascular dynamics, is composed of grants that support studies designed to establish explanations for normal function. These studies must precede an understanding of disease states, since the information they provide becomes the basis for the formulation of methods of disease detection and diagnosis, and the design of instruments and procedures. They define the required action of drugs for the prevention, control and treatment of diseases. This research area interrelates strongly with the programs in this and other branches. As work progresses on many of these grants, they tend to evolve and to change their emphasis from elucidation of basic mechanisms to application of this information to the study of cardiovascular disease. As they do, the grants are transferred to other, disease-specific programs of the Institute.

The expenditure of funds on grants in the Cardiac Diseases Branch has continued to increase above the low of FY 1970 for the second year. The total amount in FY 1972 was $23.4 million, a net increase of about 15 percent over the previous year. This increase was not distributed uniformly across the research areas of the branch, however. In fact the funding in some areas actually declined. There was also a decline in the total number of grants in the Branch, for the fourth consecutive year (about 5% below FY 1971). In spite of this reduction to 432 active grants, more were paid in the three research areas that experienced an increase in funding. The two research areas that had reduced funding accounted totally for the decrease in the number of funded grants.

Cardiac Arrhythmias: This research area deals with the processes by which the rate, rhythm and coordination of cardiac activity are regulated; and with disorders in this system, their nature, manifestations, diagnosis, prevention, control and treatment. This system is usually studied and evaluated on the basis of measurements of electrical activity. Direct electrography, which a few years ago was strictly used in animal experimental studies, is increasingly being used to assess human cardiac conduction defects using catheter electrodes. Decisions regarding method of treatment are now being made on the basis of these measurements. Major multidisciplinary efforts in several laboratories are directed toward multiple electrode body surface mapping in an attempt to provide the data for the development of a clinically useful cardiac depolarization model. These, along with novel analytical approaches in scalar- and vector-electrocardiography and some new studies in magnetocardiography, constitute a large portion of this research area. The latter should provide an analysis of low frequency activity and activation events which have peculiar spatial orientation and are, therefore, relatively silent using the usual measuring techniques. These methods of measurement are different approaches to the evaluation of the same activity. Some provide more useful information in certain conditions than others. One of the major objectives is to find new approaches that will provide unequivocal, theoretically based evaluations of this aspect of heart activity.

Additional studies are directed toward analysis of the role of arrhythmias in sudden cardiac death. There is strong reason to believe that electrical instability of the heart, as manifested by arrhythmias, possibly of an as yet undetermined but specific form, may be responsible for the precipitation of this crisis state. By defining the predisposing conditions it may be

possible to develop prediction, prevention and treatment methods.

Instrumentation programs for the design of pacemakers, defibrillators and cardiac resuscitation devices; basic studies in cardiac electrophysiology; and finally, a major effort, the assessment and development of drugs useful for the treatment and prevention of arrhythmias are also major elements in this grant program.

This is an extremely active area of research. The number of grants in it has grown steadily over the last three years; and further growth is likely. FY 1972 funding was $2.5 million for 62 grants.

Cardiac Diseases: In this research area are included the largest proportion of the Institute's grants on heart disease having other than ischemic, congenital or rheumatic origins. As a consequence, the grants cover a wide variety of cardiac pathological states. In it are studies on various forms of cardiomyopathy, diagnostic indices of abnormal cardiac function such as heart sounds and murmurs, and the effects of various agents, drugs, toxins, and trace metals on the structure and performance of the heart. In the past year, this program has experienced substantial growth, largely as a result of the transfer into it of a few large grants from other programs of the Institute. One of these is a clinical data retrieval/data processing proposal, which complements others of that type that are already in this program area. FY 1972 funding was $4.4 million for 49 grants.

Cardiovascular Dynamics: This research area is the most diverse, as well as the largest in the branch, 170 grants. It contains proposals to do basic research on almost all aspects of the cardiovascular system. Included are studies of cardiac biochemistry that range through energy metabolism, enzymology, the chemistry of contractile proteins (of heart, skeletal and smooth muscle) and molecular aspects and chemistry of contraction. In combination, these studies are designed to define the normal chemical state of the heart and its operation in the absence of pathology. They, like all basic studies, provide a quantitative picture of health, the yardstick with which disease is measured. They define the objective state that all therapy must be designed to achieve, that all preventative measures must be designed to maintain.

Studies on excitation-contraction coupling are supported here. This is the transduction process which bridges the gap between the ionic transfers that take place during activation, and the biochemical structure of heart (or other) muscle which leads ultimately to shortening, tension development and the performance of mechanical work. Hence, the dynamic performance of the heart, as a muscle and as a pump, is tied to the activation and transduction processes. It is likely, too, that the mode of action of critical pharmacological agents (such as the cardiac glycosides) will be found through the studies in this area and that the structure of future drugs will be fashioned on the basis of the information provided by this work.

Grants directed at the analysis of the dynamic function of the heart in animals and in normal and diseased humans are a part of this program. In increasing numbers, active efforts are being directed to these analyses

using catheterization procedures, cine-angiography, video-densitometric techniques, and non-invasive measurements like the assessment of systolic intervals and others. The ultimate goal is to provide safe, reliable procedures for the evaluation of human ventricular performance; and to determine appropriate therapy in disease states based on these measurements. To this end, at times alone, but often in association with these clinically directed researches, investigators pursue studies on the fundamental aspects of muscle (cardiac, vascular and sketetal) contraction.

The remainder of this research area is composed of grants on peripheral circulatory dynamics; the function and activities of the microcirculation in providing nutritional blood flow to the tissues and organs of the body; the quantitation of perfusion in collateral and shunt vessels and their development and contribution in conditions of embarrassed or inadequate local blood supply; rheological properties of blood; viscosity and drag reducing blood additives that may be of importance in in vivo conditions of turbulent flow, during extracorporeal perfusion or with the use of vascular prostheses; the control of the cardiovascular system: neural, hormonal, humoral elements, central vs local control, and integration of cardiovascular functions.

This large, valuable and diverse program area is growing at a rapid rate as investigators combine research activity that is directly applicable to human disease with fundamental studies that provide the clues to new bases for understanding, diagnosis, prevention, control and treatment of these pathological states. Funding increased 38 percent over last year and eight percent more grants were added to this research area.

Heart Failure and Shock: The Institute's support of heart failure research includes studies of hypertrophy, RNA and protein synthesis in the myocardium, the metabolism of the failing heart, the pharmacological action of digitalis glycosides and the metabolism and excretion of these agents, autonomic control and the action and metabolism of sympathomimetic amines, contractile performance of the failing ventricle, and hemodynamics and venous return in heart failure.

The Cardiac Diseases Branch is also the focus for administration of grants for research on all forms of shock: hemorrhagic, traumatic, burn, and septic. Support is provided for studies on the mechanisms, treatment and responses of animals and man to the shock state.

Funding in these research areas has declined in the past few years. The number of grants funded in FY 72 declined by 21 percent to 117 and the funding by six percent compared with the previous year. This may reflect the fact that no major breakthroughs have resulted from these studies. The funding reduction is not the result of expansion of similar programs in other institutes. NIGMS's trauma center activity is also declining, with two of the present eight centers being phased out. NIAID's program related to spetic shock is directed toward studies on micro-organisms, not to the cardiovascular or respiratory aspects of the shock syndrome.

Congenital and Rheumatic Heart Disease: This subsection of the Branch is the Institute's major program supporting research on heart diseases in

children. Rheumatic heart disease, which has its greatest prevalence among the poor, is the most common, serious, preventable form of heart disease. The incidence of pediatric cardiac death has declined in the past decade, about 30 percent from rheumatic fever and rheumatic heart disease and more than 5 percent from congenital heart disease. Both however, remain important health problems.

Surgical studies in both research areas are directed toward perfection of existing techniques and devising new ones for the repair of defective or diseased hearts. Studies are supported on the production of new kinds of cardiac valvular prostheses and development of new surgical techniques for their placement or for the repair of damaged heart valves. There are also grants that deal with diagnostic procedures: ECG; body surface mapping; hemodynamics in children and, increasingly, in fetuses as well; the development and application of new noninvasive diagnostic procedures (ultrasound valve motion studies, for example). A unique canine colony that develops congenital heart disease is supported as are a limited number of fundamental studies of the chemistry and contractile performance of diseased hearts and the mechanism of production of rheumatic heart disease by the streptococci. Studies of improved treatment methods are also supported.

Total support in this area remained essentially constant in the past two years, but declined sharply to 34 grants in FY 1972. Funding was reduced by 27 percent and the number of grants by 34 percent.

HYPERTENSION AND KIDNEY DISEASES BRANCH. The branch supported 208 grants this year. Sixty-two of them were in the area of renal function and disease, 14 in fluid and electrolyte studies, and 135 on the many aspects of hypertensive vascular disease. These include 6 program projects and 5 specialized centers. The total cost for these grants ran over $14.7 million. In another branch, the institute initiated a clinical trial study on hypertension and continued support for a clinical cooperative study on the treatment of essential hypertension.

Hypertension: This was the first year for the Specialized Centers of Research in Hypertension. Because of the complexities involved, it was several months after the June 1, 1971 starting date before they were in full operation. This promises to be a fruitful mechanism for the support of research. Several cooperative arrangements have been made among the centers which will promote advances in each. Some particular aspects of the hypertension problem are being checked in all centers because of preliminary findings which were reported at an early meeting of the group. Because they expressed a need for a resource of standard reference antibody for Angiotensin-I assays, the project officer, in conjunction with the chairman of a similar committee appointed by the American Heart Association, is exploring possible development of such a resource. An advisory committee was established late in the year to assist the institute in evaluating and guiding this program. It will meet for the first time early in the new fiscal year. Each center will be visited once each year by members of this committee, plus any ad hoc consultants necessary

to get an in-depth picture of progress in each center. Members of the committee will also meet once each year with the Directors of the centers.

Further progress is being made in analyzing the interrelationships between the renin-angiotensin-aldosterone factors in hypertension and in other regulatory mechanisms which are involved. The development of, and modification and improvements in, radioimmunoassay methods for Angiotensin-I and II and Aldosterone have made possible more accurate quantitative determinations of these substances in hypertensive patients. When done carefully under well-controlled conditions in the patients, interesting leads are being obtained. One group reported recently that they had no cases of heart attack or stroke in hypertensives with low plasma renin activity. It has been known for some time that large doses of renin or Angiotensin-I produce damage to blood vessels, but no evidence has been accumulated showing that the chronic presence of more moderate, functional levels of these substances will lead to damaged vessels, especially in conjunction with hypertension. If this work is substantiated, it must be assumed that finding a means of lowering plasma renin activity could sharply lower the rate of occurrence of cerebral and coronary accidents in hypertensives.

Renal Disease. Probably the outstanding development during the year was expanded research and interest in renin obtained from the sub-maxillary salivary gland. The concentration here is several times that in the renal cortex, and two groups have indicated that they have been able to purify renin obtained from this source and are starting to study its structure. More evidence is accumulating to demonstrate that alteration in body fluid compartments are a primary factor in the hypertensive process. How the kidney responds to or is responsible for these changes is being studied extensively. Progress on this problem continues, but so far only moderate advances are recognizable. Much of the research supported in these grants concerns a better understanding of the functioning of the kidney in health and disease. Methods are being developed for estimating regional blood flow within the kidney. This should make it possible to determine how changes in volume of flow within the kidney is regulated. Considerable emphasis is being placed on the glomerular basement membrane since it seems to be or primary importance in several diseases of the kidney. We support one program project on transplantation with primary emphasis on the kidney. However, this group can claim the oldest transplanted heart still living (over four years) with no rejection episodes during the last year.

Fluids and electrolytes: The research in this area is closely related to both hypertension and kidney disease. Some fluid and electrolyte research is a component of many grants in those areas and there are some reports indicating that changes in body fluid compartments is of primary pertinence to the development of hypertension. We support one program project in this area covering a broad research program in fluids and electrolytes with emphasis on the role of cell membranes in their exchange.

PULMONARY DISEASE BRANCH. The incidence and prevalence of acute and chronic respiratory conditions, especially chronic obstructive diseases such as emphysema and bronchitis, is widespread in the U.S. population. These diseases are complex and are intimately involved with other circulatory

and organ systems. The Pulmonary Disease Branch administers regular research grants, pulmonary program project grants, and Specialized Centers of Research which focus on diverse and multidisciplinary efforts to establish the causes, effects and treatment for the various respiratory disorders.

During Fiscal Year 1972, the Pulmonary Disease Branch supported 177 research grants for $6.9 million, 7 pulmonary program projects for $2.2 million, and 11 SCOR programs for $4.7 million. Six additional Specialized Centers of Research in pulmonary disease were established following a second round of competition for center support ($2.4 million). The seventeen centers support multidisciplinary research with emphasis on clinical programs which are designed to bridge the gap between basic research and clinical care. The major efforts of the SCOR programs are directed toward respiratory distress syndrome of the newborn, and adult respiratory diseases such as chronic obstructive lung disease, interstitial and diffuse pulmonary disease and respiratory distress syndrome in the adult. The six new SCOR programs will focus on granulomatous disease, chronic interstitial pneumonia, hypersensitivity pneumonitis and response of the lung to injury.

The variety of research supported by individual research grants and program project grants ranges from the most basic studies in pulmonary structure and function to multidisciplinary clinical and epidemiological description of respiratory disease. The research activities of the program have been classified by disease category. Current activities within each category will serve to emphasize progress which was made and new activities which were initiated during the year.

Diseases of the Airways: A significant portion of acute and chronic diseases of the lung affect the airways. In the current lung program, research efforts are directed toward studies of airway diseases including asthma, bronchitis, bronchiectasis, bullous disease, emphysema and alpha-1-antitrypsin deficiency. There are 56 regular research grants for $1.7 million in this category. Two program project grants have major research emphasis in this area ($422,000). Furthermore, 15 projects within 9 SCORs are directed toward research problems associated with diseases of the airways.

One of the major areas under investigation is the study of the etiology of chronic bronchitis and emphysema. An association between alpha-1-antitrypsin deficiency and pulmonary emphysema has been demonstrated. To date, nine different variants of the alpha-1-antitrypsin have been identified by methods involving phenotyping which is time-consuming, expensive and not readily adaptable for screening large populations.

Recently, however, a new method was devised which shows great promise for detecting the deficient alleles even in the presence of normal serum antitrypsin activity and concentration. The method, which involves the formation of a double ring antigen-antibody precipitation pattern, can be performed rapidly on many specimens per day and represents a major contribution towards understanding the mechanism of alpha-1-antitrypsin deficiency and the development of pulmonary emphysema.

Patients with established pulmonary disease, relatives of these patients and volunteer subjects have been screened to assess the role of alpha-1-antitrypsin deficiency in the development of chronic broncho-pulmonary disease, establish criteria for predicting an individual's susceptibility to lung disease and develop strategies for the prevention and treatment of such disease. Antitrypsin deficient individuals have been identified among presumably healthy subjects; these individuals showed early but definite evidence of obstructive lung disease. Irregardless of smoking history, abnormalities suggestive of anatomic emphysema were more common in individuals with antitrypsin deficiency than in controls. These findings support the concept that obstructive disease in antitrypsin deficiency arises from the interaction of genetic and environmental factors. Anatomic emphysema may result from the deficiency. Such lesions need not produce symptomatic obstructive disease, but could render an individual susceptible to harmful environmental factors.

Major research emphasis has been placed on pathophysiologic mechanisms in chronic obstructive pulmonary disease in order to understand the major clinical problems of patients, exercise limitation, episodes of respiratory insufficiency and factors leading to changing obstruction and ventilation-perfusion relationships.

Interstitial and Diffuse Pulmonary Disease: A large number of respiratory disorders affect the pulmonary interstitium and alveoli. Almost 200 different syndromes are identified as interstitial diseases including allergic, congenital, metabolic, neoplastic, infectious, and unknown origin as well as those related to occupational exposure, systemic diseases, external physical agents (e.g. radiation) or drug toxicity. During FY 1972, the branch supported in this category nine research grants for $357,000, subportions of three program projects for $57,000, and two projects in SCOR for $160,000. Furthermore, major portions of the six new SCOR programs will focus on research in this area.

Sarcoidosis is the most prevelent of the non-infectious granulomatoses. Although not a major cause of death, sarcoidosis is a common cause of suffering and disability in early and middle adult life. Like most other granulomatoses, it may involve distant parts of the body, but its most important involvement is pulmonary. Sarcoidosis, which appears to play a role greater than has been appreciated in the genesis of subsequent disability and illness due to pulmonary cyst and fibrosis, is a disease which occurs 10-15 times more often in black than in white Americans.

Researchers have successfully developed an intracutaneous test (the Kveim test) for the diagnosis of sarcoidosis. Sarcoid clinics have been formed in an effort to elucidate the etiology and pathogenesis of the disease. For example, a substantial roster of patients with sarcoidosis has been developed at the sarcoid clinic at Mt. Sinai Hospital in New York where the research objective has been centered around a systematic effort to isolate by physical, chemical, enzymatic, immunologic and radioimmunoassay techniques the active principle or principles present in human sarcoidal tissue suspensions. Isolation and identification of the active fraction responsible for evoking the characteristic epitheloid granulomas will

promote earlier and more accurate diagnosis and more effective treatment of the disorder, which will help to reduce the frequently crippling effects of end-stage sarcoidosis with its dreaded complications of pulmonary and renal insufficiency and blindness.

Thermophilic actinomycetes are suspected to be the offending contaminants of several organic dusts which are associated with the development of a hypersensitivity pneumonitis such as farmer's lung. Recently, investigators, supported by NHLI, studied a number of patients who developed hypersensitivity pneumonitis after inhaling thermophilic microorganisms growing in contaminated furnace humidifiers, portable room humidifiers, or contaminated air-conditioners. These patients contracted the disease without being exposed to any well-defined organic dust. It was shown that the species of thermophilic actinomycetes isolated from the home environment differ from the usual thermophiles found in organic materials. These studies on hypersensitivity pneumonitis will be continued and expanded in one of the new SCOR programs. Three institutions in Wisconsin, an area with high incidence of farmer's lung and other hypersensitivity lung diseases, will combine facilities, expertise, and clinical material in an in-depth study of the etiology, pathogenesis, and treatment of these diseases.

Vascular Diseases: The Branch sponsors research programs in many facets of pulmonary vascular disease: pulmonary hypertension and cor pulmonale; thrombotic and fat embolism; and pulmonary edema. Programs related to acute respiratory distress syndromes in the adult and neonate are also classified within this group which contains 45 research grants for $1.4 million, 12 programs within program project grants for $235,000, and 5 projects in SCOR for $380,000.

The high morbidity of pulmonary embolism in this country (more than 6,000 deaths per year) indicates that this disease is a significant public health problem. Several research programs focus on the diagnostic assessment of patients suspected of having thromboembolism. Lung scans and determination of arterial pO_2 have been shown to be excellent screening procedures; the more complicated procedure of pulmonary angiography is reserved for those who have positive scans and reduced arterial pO_2. Results of pulmonary function tests indicate that acute pulmonary embolism causes a decrease in vital capacity and total lung volume. The ratio of residual volume/total lung capacity increases and steady-state diffusing capacity is low. These abnormalities help to distinguish pulmonary embolism from chronic lung disease and/or congestive heart failure. Furthermore, determination of fibrinogen-split products (FSP) offers considerable promise in the early detection of pulmonary embolism since investigators have been able to detect FSP in serum of patients with pulmonary embolism proven angiographically. Fibrinogen-split products were not present in most clinically normal patients (29/30 patients) and were not present in patients with thrombophlebitis without pulmonary embolism. Future investigations will establish whether the appearance of FSP in serum will allow detection of pulmonary embolism prior to the onset of diagnostic symptoms.

Mammalian lungs are lined with a surface active material which may help to prevent alveolar collapse at small lung volumes. Reduced quantities of this material are associated with lung collapse observed in hyaline membrane disease. Investigators are currently attempting to establish the factors responsible for the regulation of phospholipid and protein metabolism associated with the biosynthesis of this surface active lipoprotein. The preponderance of evidence indicates that this material is a lipoprotein with a high content of dipalmitoyl phosphatidyl choline, a phospholipid which is one of the most potent surface active agents known.

It has been determined that the human fetal lung has as much surfactant per kilogram of body weight as the adult by 22 weeks gestation. Although there is a great surplus of surfactant in fetal lung tissue relative to available lung surface area as early as 22 weeks gestation, the pulmonary factor limiting adaptation to air-breathing is probably the transfer (by secretion) of surfactant stored in the tissue onto the alveolar surface. A rapid sensitive test for surfactant in amniotic fluid has been devised. Fluid from 93 women with complicated pregnancies, drawn within 24 hours of delivery, yielded 68 tests positive for surfactant (all infants were healthy), 13 intermediate tests (8 infants had respiratory difficulty), and 12 negative for surfactant tests (11 infants had severe RDS and 1 had transitional respiratory distress). This is an excellent illustration of the application of fairly basic research to clinical problems. The obstetrician and pediatrician will be able to predict with reasonable accuracy the chances that a fetus, if delivered too soon, will develop the respiratory distress syndrome. This test should help to reduce neonatal mortality.

Chronic Hypoxemia and Pulmonary Transplantation: A given disease may cause hypoxemia through one or combinations of the following physiologic alterations: alveolar hypoventilation; maldistribution of ventilation and perfusion; anatomical right-to-left shunting; and impairment of diffusion. Researchers supported by the NHLI lung program are studying a number of problems of chronic hypoxemia that result from such physiologic alterations in disease states. The program has 45 research grants for $1.3 million, 2 program projects for $517,000 and 8 projects within the SCOR program for $600,000.

Respiratory failure claims the lives of several hundred potentially salvageable patients every day. Even when aided by respirators, antibiotics and enriched oxygen concentration, many patients fail to sustain adequate pulmonary function and die of progressive hypoxia, hypercapnia and acidosis. In an attempt to establish the reasons for this, NHLI supports many basic programs in respiratory physiology. For example, investigators are considering the control of ventilation, control of pulmonary circulation, and oxygen transport systems. Much of the foundation for understanding respiratory disease will come from these basic research programs.

Inability to maintain adequate blood and tissue oxygen levels because of chronic pulmonary disease may be one of the indications for pulmonary transplantation in the future. Investigators are now working on problems of rejection phenomena and organ preservation in experimental models.

Furthermore, experimental animal models for lung transplantation have provided information on pulmonary blood flow in reimplanted lungs. Although excision and reimplantation of the lung temporarily reduces pulmonary arterial blood flow to the lung in experimental animals, investigators have demonstrated that blood flow to the reimplanted lung is 59% and 73% of preoperative measurements 2 days and 2 weeks, respectively, after operation. Part of the reduced flow is due to postoperative congestion, atelectasis and edema; however, edema and inflammation around the pulmonary veins and left atrial anastomosis also contribute to the increased vascular resistance in some animals. Six weeks after operation, blood flow to the reimplanted lung was 90% of preoperative measurements and was not significantly different. Data obtained from projects such as this are prerequisite to the study of physiologic and pharmacologic means to alter blood flow in denervated and partially reinnervated transplanted lungs.

Progress in lung transplantation depends not only on further advances in the field of transplantation in general, but also on overcoming several difficulties specific to the lung itself. Suitable methods must be developed to perfuse the lung in situ. One NHLI supported investigator is currently evaluating a method of lung preservation based on the perfusion of bronchial vessels rather than that of the pulmonary artery. The perfusion system consists of a small pulsatile pump, feeding from a disc-oxygenator through a flow meter into the aortic cannula. Results indicate that isolated bronchial perfusion is indeed feasible and represents a desirable feature in any method which is aimed at preserving lungs before transplantation.

Environmental Diseases: The lung program includes research activities directed at several inhalation diseases in man including those related to noxious gases, inorganic and organic dusts and the study of symptoms related to altitude and hypobarism. This section includes 19 research grants ($440,000), 3 program project grants ($709,000), and 5 projects in SCOR programs ($220,000). A major emphasis in this program is to determine how exposures to unusual environments favorably or unfavorably affect the health of man.

The lung program supports three programs involving research with hyperbaric chambers. Among the unusual environments given particular consideration for research by NHLI supported investigators are: increased or decreased barometric pressure, altered breathing media, immersion, and altered environmental temperatures. The potential range of scientific applications for the type of research conducted in hyperbaric chambers includes: determination of how modifying external environmental atmospheric pressure, gaseous composition and temperature can exert a beneficial action upon human illnesses with or without concurrent additional measures to support life; investigations of how biologic processes and performance in marine animals, land animals and man are modified by exposure to selected dry or liquid environments in which hydrostatic pressure, gaseous composition and temperature are selected variables. In the hyperbaric chambers, hydrostatic pressures can be simulated beyond those present in the deepest portion of the continental shelf.

Diseases of the Neuromuscular Apparatus: Abnormalities of neural or muscular function may interfere with pulmonary ventilation and lung function, although no primary abnormality exists in the lung. This type of disease represents only a small part of the total pulmonary disease problem. Thus, this section has only three regular research grants for $69,000 and two projects in program project grants for $25,000. Programs in this area include studies on the manner in which disorders affecting the spine or chest wall affect pulmonary function and the effect of vagal nerve stimulation on various respiratory reflexes.

SPECIAL PROGRAMS BRANCH.

The Special Programs Branch serves a unique function within the extramural activities of the Heart and Lung Institute. The branch supports research grants in four circumscribed areas of NHLI interest and administers a large number of multicategorical program project grants. In addition, the branch is responsible for the initial review, usually entailing a project site visit, for virtually all program projects (categorical or multi-categorical) submitted to the Institute. Fiscal year 1972 grant funds for this branch total over $22,500,000.

Artificial Devices ($3,890,000)

Recently, the scientific community and the Heart and Lung Institute have expressed strong interest in providing more basic engineering input into the problems associated with the development and testing of artifical cardiac and pulmonary support systems. This interest is reflected in the start of two large program projects in this area. One is quite basic; studies at this institution involve the characterization and development of nonthrombogenic surfaces, studies of the structure of natural and synthetic membranes, theoretical studies of transport and control mechanisms in the cardiovascular system, and the development of novel instrumentation methods especially suited to the study of biological materials.

The other program project's activities are somewhat more applied, involving the design, implantation, and engineering and physiological study of artificial circulatory assistance devices in animals. Significant progress has accrued in this field within the last year. Calves, totally supported by an artificial heart, are routinely surviving for 7 days; one animal has remained alive for 2 weeks. Although these survival times are relatively short compared to long-term goals, they are important in that they allow for a stable animal preparation suitable for detailed hematological and physiological studies, from which information can then be utilized in the improvement of engineering aspects.

The two larger programs are in company with a number of existing and new smaller, regular research grants.

The Institute anticipates rapid development in this field. Probably at least three new "biomaterials/artificial devices" program projects will begin next year. Increasing quantities and quality of regular research

grant applications should be commensurate. Significant progress in basic biomaterials study, design and testing of improved partial circulatory assist devices, membrane oxygenators and the total artificial heart should be forthcoming.

Transplantation ($1,212,000)

The Institute supports a number of basic and animal studies of cardiac and lung transplantation and one large program in clinical cardiac transplantation.

The staggering early mortality of human patients with lung transplants has added an even greater emphasis to experimental work in this area. Lung transplantation is still hindered by technical surgical problems; these must be resolved in the laboratory animal before any significant degree of clinical success can be anticipated. Most investigators believe that massive rejection has accounted for a number of early clinical failures; hence, the pathogenesis of this rejection as applied to the lung is under vigorous study. Finally, the transplanted lung exhibits grossly altered pulmonary physiology; the reasons and corrections for this pathophysiological state are also being pursued.

The Institute supports a small, but broad-based program in cardiac transplantation. Especially promising are some of the investigations attacking the problem of rejection. For instance, early studies dealing with modification (irradiation, immunosuppressive agents) of the donor heart show signs of improving survival times of the recipient animal. Antilymphocyte globulin (ALG) treatment of the recipient also appears to be beneficial.

One clinical program for cardiac transplantation is funded by the Institute. This group embraces the idea that a small, well-controlled investigative program of clinical cardiac transplantation is important. The Institute supports this concept. A small number of highly selected, very carefully studied patients are receiving transplants. Not only has this group's survival record been excellent, but important immunological and physiological data are resulting from the study of these patients. A strong program in animal transplantation is also being pursued by this group.

The Institute believes that its grants program in transplantation is a sound one; for the present, the major effort is in the laboratory along with selected, small scale clinical evaluations.

Fundamental ($1,284,000 including Behavioral funds)

Grants in this area are those of a basic science nature, primarily biochemical, which are supportive of many programs of the Heart and Lung Institute. Studies of the biochemical events of muscle contraction, molecular energy production and oxygen carrying proteins are examples of such fundamental investigations. The relevance to clinical problems of congestive heart failure, cardiac hypertrophy and disorders of hemoglobin structure/function is obvious.

Behavioral

The primary objectives of research in this area are to clarify the role of behavioral and environmental factors in the pathogenesis of cardiovascular and pulmonary disease. Behavioral control of cardiovascular function (visceromotor learning) is beginning to be appreciated by an increasing number of cardiologists and cardiovascular physiologists. Operant and respondent conditioning techniques are used to establish and maintain behavior repertoires in primates and carnivores; concurrent measurements of the circulation and behavior provide a basis for assessing the selective role of classical physiological mechanisms in the initiation, regulation and maintenance of cardiovascular responses (cardiac output, blood pressure, etc.) to the environment. In man, patients are being taught to voluntarily control systolic blood pressure.

The future application to clinical situations of controlling or preventing arrhythmias, hypertension or altered vasomotor states is intriguing, though much basic physiologic work is still needed.

Multicategorical ($16,104,000)

Multicategorical grants are those which encompass several categorical areas of interest of the Institute. They are usually program projects that involve a number of cooperating investigators, frequently of differing disciplines. Such interdisciplinary endeavors bring the talents of a diversity of medical specialists (physicians, surgeons, pediatricians), basic scientists (physiologists, biochemists), and bioengineers together to focus on broad problems of cardiac or pulmonary diseases. Because of their multicategorical nature, the efforts of these several disciplines can be brought upon problems not neatly falling into a strictly "categorical" interest of the Institute. Such a group tends to form a stable base of cardiopulmonary research at an institution through shared equipment, patient populations, or intellectual resources. These grants also frequently involve fundamental and clinical research and, hence, foster rapid scientific exchange between the basic scientist and clinician.

These grants provide research institutions with a mechanism for fostering broad-based approaches to problems of cardiopulmonary disease.

THROMBOSIS AND HEMORRHAGIC DISEASES BRANCH. Disorders of the blood or blood vessel system are among the most important factors underlying a disease process or traumatic injury. It is recognized in this country that thrombosis and hemorrhage may well exceed any other group of pathogenetic mechanisms causing or contributing to mortality and morbidity in our population. Thrombosis and hemorrhage which represent the two opposing extremes in blood, as well as all gradations of both phenomena and their interaction with the natural and artificial vessel wall, are the prime research targets of the Thrombosis and Hemorrhagic Diseases Branch.

In addition to this major charge, the Branch has responsibility for projects pertaining to the liver, spleen, and other lymphoid tissues as they involve phagocytosis and other functions of the reticuloendothelial system. By far,

however, the greatest emphasis is on blood components and blood diseases as reflected by the current number of grants (259) and funds ($16,286,776). Nine (9) grants currently support studies on hepatic structure, function and disease for $346,596, while five (5) grants support reticuloendothelial studies for $203,537. Although these latter two areas are small in numbers of grants and dollars, they are important as complementary research to a vigorous contract program within another Branch of this Institute.

Since the turn of the new decade, 1970, funding for projects within the Thrombosis and Hemorrhagic Diseases Branch has increased by $6 million, more than $2 million of which was awarded for Special Centers of Research during FY 71. Last year (FY 71) 269 grants were funded for $14 million. A total of 273 grants were awarded this fiscal year '72 for around $17 million. Consequently, the history of this Branch shows a steady growth in numbers of grants, funding and new programs.

A broad spectrum of studies ranging from basic research to clinical research on diseases of the blood and blood vessels is being supported by the grant mechanism (project, program project, SCOR, cooperative program). Subjects of research include the formed elements of the blood, lymphatic, bone marrow and other bloodforming tissues, as well as hemoglobin, coagulation components and subcellular elements of the plasma which involve blood coagulation and lysis. Some examples of approaches being used and developed are molecular, genetic, immunologic, histochemical, biochemical, biophysical, structural and functional.

While general progress was made along a broad front this past year, some significant advances stand out in several specific areas. Noteworthy are the following:

Diagnostic Methods: At Columbia University, a very promising radioimmunoassay for thrombin fibrinopeptide A and B is being developed, which could be highly important clinically for the diagnosis of ongoing intravascular coagulation. The quantitation of fibrinopeptide A would allow the degree of activation of the coagulation system in patients to be determined. This information would help resolve the uncertainties about the occurrence of disseminated intravascular coagulation in human patients and provide a basis for rational therapeutic measures.

Fibrinogen and Fibrinolytic System: Important information is coming from studies in a European laboratory elucidating the structure of fibrinogen, which is providing a framework for the understanding of the fibrinogen molecule in hemostatic reactions. This research also extends into areas which involve the mechanism of enzyme action, protein evolution, the molecular basis of disease, intravascular coagulation, fibrinolysis, and the development of chemical techniques of amino acid sequencing.

Studies from a New York laboratory on the effect of collagen on the fibrinolytic system indicate an "anti-coagulant" role of collagen vis-a-vis known procoagulant effect on platelets, Factors X, Xa, and XII, thereby reflecting collagen function in the "clotting balance."

An interesting lead, which is being followed up, is the observation that upon traumatic injury to the brain and head, marked defibrination of the blood occurs, predisposing to massive hemorrhage. A study is being mounted to answer specific questions about the extent and duration of intravascular coagulation in various types of head injury and to examine the possibility that hemostatic failure contributes significantly to the pathogenesis of intracranial bleeding of the head injury. This could lead to a change in the initial emergency treatment for such injuries and subsequent management.

Red Cells-Hemoglobin: Work on the destruction of red blood cells in a California laboratory has yielded significant and fundamental advances in the identification and purification of proteins involved in hemoglobin catabolism, in particular, hemopexin. This work is especially relevant to the hemolytic anemias such as sickle cell anemia, thalassemia major, pernicious anemia, paroxysmal nocturnal hemoglobinuria and porphyria.

The development of the brine shrimp as a model to study the composition and production of hemoglobin as well as its control mechanisms holds promise of becoming a powerful tool for elucidating the genetic control of hemoglobin synthesis, thus contributing to our understanding of the evolution of hemoglobin structure and function. The brine shrimp is a choice animal since its three hemoglobins are an ideal system for assay of regulatory mutations because 1. the hemoglobins are inducible; 2. they are not essential for life; 3. changes in quantity can be detected in the living, transparent animal; 4. the shrimp is suitable for genetic studies; and 5. the hemoglobins are easily isolated for biochemical studies.

Platelets: Outstanding research has been done on platelets in a New York laboratory dealing with platelet aggregation and release reaction induced by Zymosan. This work relates the platelet release reaction to the immune mechanism and activation of the plasma complement system as another physiologic and possibly pathologic pathway of platelet aggregation and agglutination.

Blood Factors: Important information on Factor V, its activation, role in the clotting sequence and interaction with Ca^{++} is originating from a Boston laboratory, which will provide insight into some of the chemical changes which accompany diffuse intravascular coagulation that underlies thromboembolic phenomena. Factor V was selected because it is a single protein and necessary for thrombin formation. Also, in turn, it can be activated by thrombin. It is believed that this positive feedback may constitute an important regulatory mechanism.

Tissue Factors: Research conducted at Yale University has contributed to the further understanding of the role of tissue extracts in the extrinsic pathway of blood coagulation. The data collected from these studies support the concept that the peptidase and coagulant activities are functions of the same molecule, and that tissue factor may function biolcgically through a proteolytic mechanism.

Hemophilia: Advances are being made in the treatment, diagnosis and general understanding of hemophilia. This Branch presently administers 33 grants dealing with this area for a little over $1½ million. Specific progress

has been made in a Washington laboratory on the purification and characterization of Factor VIII (Anti-hemophilic-Factor).

In an Ohio laboratory a method has been developed which will differentiate immunologically between classic hemophilia (Factor VIII Deficiency) and von Willebrand's Disease. It has been observed that in all hemophiliacs there is a cross-reacting material to Factor VIII antibodies in amounts comparable to those in normal plasma. However, in von Willebrand's Disease this cross-reacting material is present in decreased amounts in proportion to the functionally active Factor VIII. Therefore, von Willebrand's Disease may represent a lack of Factor VIII while classic hemophilia is characterized by abnormal Factor VIII. This same laboratory is also able to diagnose the carrier state of hemophilia in pregnant women by observing whether there is a proportionate rise in antigens to the rise in titer of antihemophilic factor which follows exercise and accompanies pregnancy.

Thrombosis SCORs: In fiscal year 1971 five Specialized Centers of Research were established in the thrombosis area. These were at Temple University, Wayne State University, University of North Carolina, Washington University, and Beth Israel Hospital, Boston. Each of these includes a broad range of research in thrombosis and hemorrhagic diseases and in each a considerable part of the first year of operation has been spent in staffing and tooling up. In addition to the developing research programs within each SCOR, there have been two meetings involving collaborative work among the five. Thus, in December 1971 a workshop was held in Bethesda, Maryland on newer methodology for the diagnosis of venous thrombosis. This was a 1½ day meeting involving the participation of SCOR personnel and of invited experts, some from other countries. The meeting was a highly successful exposition of the current state of development of diagnostic methodology and the conclusions of the meeting point directions for additional developmental work needed to advance this highly important area.

The second meeting was held in Philadelphia where Temple University was the host institution. The morning session of this one-day meeting consisted of a description of the research programs ongoing in the Temple University SCOR. The assembled scientists met in small groups each discussing sub-program areas (i.e., platelet research, blood coagulation, thrombolytic therapy, platelet inhibiting drugs, etc.). The Thrombosis Advisory Committee of the National Heart and Lung Institute also participated in this meeting and started developing plans for trials of platelet anti-aggregating drugs in the prevention of myocardial infarction. This meeting was held in March 1972. The next SCOR meeting is planned for September 1972.

The five Centers are funded at a total level of approximately $2.0 million Their programs complement each other. The Center at Wayne State University provides for a broad program of research including: 1) The isolation of lung and brain thromboplastins, platelet factor III and the erythrocyte lipoprotein procoagulants of animals and man; 2) study of inhibition and reversal of platelet aggregation; 3) the study of the activity of cell and vessel membranes by ultra-microscopy; 4) the isolation and characterization of coagulation factors XI and XII; and 5) the study of coagulation proteins by electron-microscopy.

The SCOR grant at Washington University provides support for about 15 interrelated projects making up a broad approach to thrombosis research. It includes both basic and clinical studies and includes some highly original projects.

At Beth Israel Hospital in Boston, Massachusetts the smallest Thrombosis SCOR has been established. Under the leadership of Dr. Deykin, there has been assembled a small team of highly original and effective investigators. Their projects include special emphasis on the study of platelet and its role in thrombosis, a radioimmunoassay for hypercoagulability, a protease inhibitor in venous thrombosis, fibrin and fibrinogen degradation products, heparin therapy, and a number of other thrombosis-related investigations.

The Temple University SCOR program in Thrombosis is also a broad program of reseach related to various facets of the problems of thrombosis. Approximately ten projects are supported ranging from basic research to clinical investigations. In the course of the year, Dr. Sherry has assembled an outstanding team of investigators and supporting personnel.

The University of North Carolina Thrombosis SCOR provides a broad spectrum of thrombosis-related research aiming toward the ultimate goals of prevention, early diagnosis and improved treatment of thrombosis. The SCOR grant provides stable support to this renowned team of investigators whose many contributions are already well known.

It is important to emphasize, however, that further expansion of the SCOR program in Thrombosis will be required before a truly national, comprehensive program can be developed.

TRAINING

The National Heart and Lung Institute, through its training grants and awards programs, has as an ultimate goal the provision of high quality medical care in sufficient quantity to meet the needs of patients with cardiovascular, pulmonary, blood, and renal diseases. This goal can be met only through continuously attracting a sufficient number of promising young trainees, providing them with high-quality training, and encouraging the most capable among those inclined towards an academic career to undertake advanced scientific training and supervised research experience. The Institute is attempting to meet these goals through its programs providing undergraduate training grants, graduate training grants, fellowships, career development awards, and pulmonary academic awards.

Undergraduate Training Grants: This year the National Heart and Lung Institute announced the discontinuance of the undergraduate training grant program, effective in Fiscal Year 1972. These grants, were initiated for the purpose of upgrading teaching in the undergraduate medical cardiovascular area and of stimulating the undergraduate's interest in this area; the funds were utilized by the recipient institutions in many ways conducive to reaching these goals. At the present time, the Heart and Lung Institute supports 96 of these programs in medical schools, 6 in schools of osteopathy, and 12 in schools of public health.

It is the consensus that many of the goals of this program have been attained and that the funds released to the Institute by their discontinuation can be utilized to better advantage. Thus, it has been determined that these funds will be used for the support of the Institute's high priority training programs.

Graduate Training Program: The graduate training programs are designed to provide support for the advanced training of physicians and scientists intending to pursue an academic career devoted to teaching, clinical service and/or research in the general areas of cardiovascular, renal or pulmonary diseases. Grants for this program are made on a competitive basis to medical schools, universities, and other research-educational organizations to assist these institutions in providing high-quality educational and training opportunities.

At the present time, the National Heart and Lung Institute is supporting approximately 270 of these programs throughout the country. Of these, 44 are in the pulmonary area, 19 in the renal area, and the remainder in the cardiovascular disease area.

Fellowships: The two primary objectives of the Fellowship program are: (1) to increase the number of trained cardiovascular and pulmonary investigators, and (2) to assure the continuing flow of skilled and imaginative research workers into the cardiovascular, pulmonary, and related fields. Promising scientists, selected on a national competitive basis, receive these awards enabling them to obtain advanced scientific training and supervised research experience. These awards serve to encourage the research interests of young persons who show promise of becoming competent research scientists; they serve to provide mature investigators with additional or specialized research experience and thus further develop their research skills. Approximately 285 Fellowships were awarded in Fiscal Year 1972.

Career Development Awards: The Career Development Award program is designed to provide stable career opportunities for scientists with outstanding potential and competence in cardiovascular, pulmonary, or renal research and teaching. This Award carries an implied commitment from the institution for long-term retention of the awardees. It supports the younger investigator or scientist of demonstrated ability who needs further experience to qualify for more senior positions. Approximately 200 awardees were supported this year.

Pulmonary Training Programs: A new emphasis placed upon the pulmonary disease area by the National Heart and Lung Institute is being supported in part through the training grant programs to which reference is made above. Although there is evidence that interest in initiating new training programs in this area is increasing, in part as a result of the new emphasis by the Institute, nevertheless, the proportional support for these programs remains small. Thus, in the graduate training grant area 44, or about 16 percent, of the grants are supporting pulmonary training. Fellowship grants support 34 individuals working in the area of pulmonary research, or about 12.5 percent of the total number of individuals supported by the Institute through this program. With regard to the Research Career Development Awardees, 37, or approximately 18 percent, are working in the pulmonary area.

A large factor tending to slow the growth of training programs in the pulmonary area is a relative lack of trained investigators and teachers. Thus, during Fiscal Year 1972, the Pulmonary Training Committee considered 65 applications for support of graduate training programs and 21 applications for Research Fellowship support. During this same period, the Cardiovascular Training Committee reviewed 124 applications for support of graduate training programs and 66 Research Fellowship applications. With this in mind, the new Pulmonary Academic Award program was initiated last year, designed in part to correct this situation.

Pulmonary Academic Award Program: This Award is designed to develop and/or strengthen the pulmonary program in schools of medicine or osteopathy and, at the same time, to provide financial support, encouragement, and opportunities for academic career growth for young physicians or scientists interested in pulmonary diseases. Each eligible institution may nominate one candidate for the Award, who must be an individual interested in devoting the major portion of his time to the development of a pulmonary curriculum and the improvement of teaching methods in this area. The Award is made for a five-year period and may be renewable for a maximum of three years.

With the limited funds available last year, the National Heart and Lung Institute was able to issue only four of these Awards. A second competition was held this year, however, and 12 additional Awards were made.

Resume of the Year: A development of particular significance in the cardiovascular area during Fiscal Year 1972 was the decision to discontinue the undergraduate training grant program. This decision was announced by the Director of the National Heart and Lung Institute at the meeting of the Undergraduate Program Directors held in Pasadena, California in June 1971. As indicated above, the directors were assured that the funds thus freed would continue to be utilized by the Institute for the support of meritorious training programs.

A highlight of the year in the pulmonary training area has been the continued development of the Pulmonary Academic Award program. Appropriate staff of the National Heart and Lung Institute have met twice during the year with the four individuals receiving Awards last year. One meeting was held at Vanderbilt University, the home base of one of the awardees, and one meeting in Bethesda. These discussions have proved helpful, both to the staff, in receiving suggestions with regard to possible improvements in the program, and to the awardees in affording an opportunity for them to discuss mutual problems with each other as well as to receive clarification from institute staff with regard to the policy, intent, and operational technicalities of the Award.

Interest in the need for and effectiveness of training grant support continues high. The National Advisory Heart and Lung Council, acutely aware of the penetrating questions being asked with regard to the continuation of support for these programs, initiated a survey of training needs in the cardiovascular and pulmonary areas and it is expected that recommendations of the Council will result therefrom.

The grant and award programs of the Extramural Research Division support a wide variety of research and training efforts. Historically, the grant and award programs have always accounted for the largest segment of the Institute's program resources. Currently some 65-70% of the Institute's funds are invested in these extramural grant and award programs. In terms of regular research project grants to support relatively well-circumscribed investigations, the NHLI program is the largest at NIH. In terms of training activities, the NHLI is second only to the National Institute of General Medical Sciences.

Approximately 2½ years ago the organizational pattern of this Division was revised to reflect major disease groups or types of activity. The allocation of research funds to particular disease areas, however, is primarily the result of the assessment of scientific merit and opportunity as determined by review groups including the National Advisory Heart and Lung Council. The allocation of research (and program project) grant support during the past three fiscal years, by program branch, is shown in Table I; several features are noteworthy. During the last three years the funds invested in arteriosclerosis research have increased by approximately $10 million. Concurrently, the funds invested in the important program area of Cardiac Diseases has increased somewhat but the percentage of total NHLI grant funds invested in this area has decreased. The growth of the Pulmonary Disease program has been most striking: comparing fiscal years 1970 and 1972, it is apparent that funds invested have increased some 2½ times and that the percentage of grant funds in this disease area have increased almost two-fold. In Hypertension and Kidney Diseases there has been some light increase in total funds but the percentage of the Extramural Research resources devoted to this disease area has remained relatively stable.

In the program area described as Thrombosis and Hemorrhagic Diseases there is included a wide spectrum of scientific endeavors ranging from the most basic elucidation of biological and chemical mechanisms to the direct application and evaluation of new modes of therapy, e.g., component therapy for various bleeding disorders. A program in Sickle Cell Disease research was highlighted in fiscal year 1972 and a total of $5.4 million was earmarked for research grants to implement this new program. This research effort has been designed to uncover new information which can be used to alleviate the suffering of a significant percentage of the Nation's black population.

The Special Program area supports multi-categorical research and studies involving such diverse elements as arificial cardiopulmonary devices, and cardiac transplantation.

The second table provides a more precise categorization of the research grants awarded during fiscal year 1972 by the National Heart and Lung Institute.

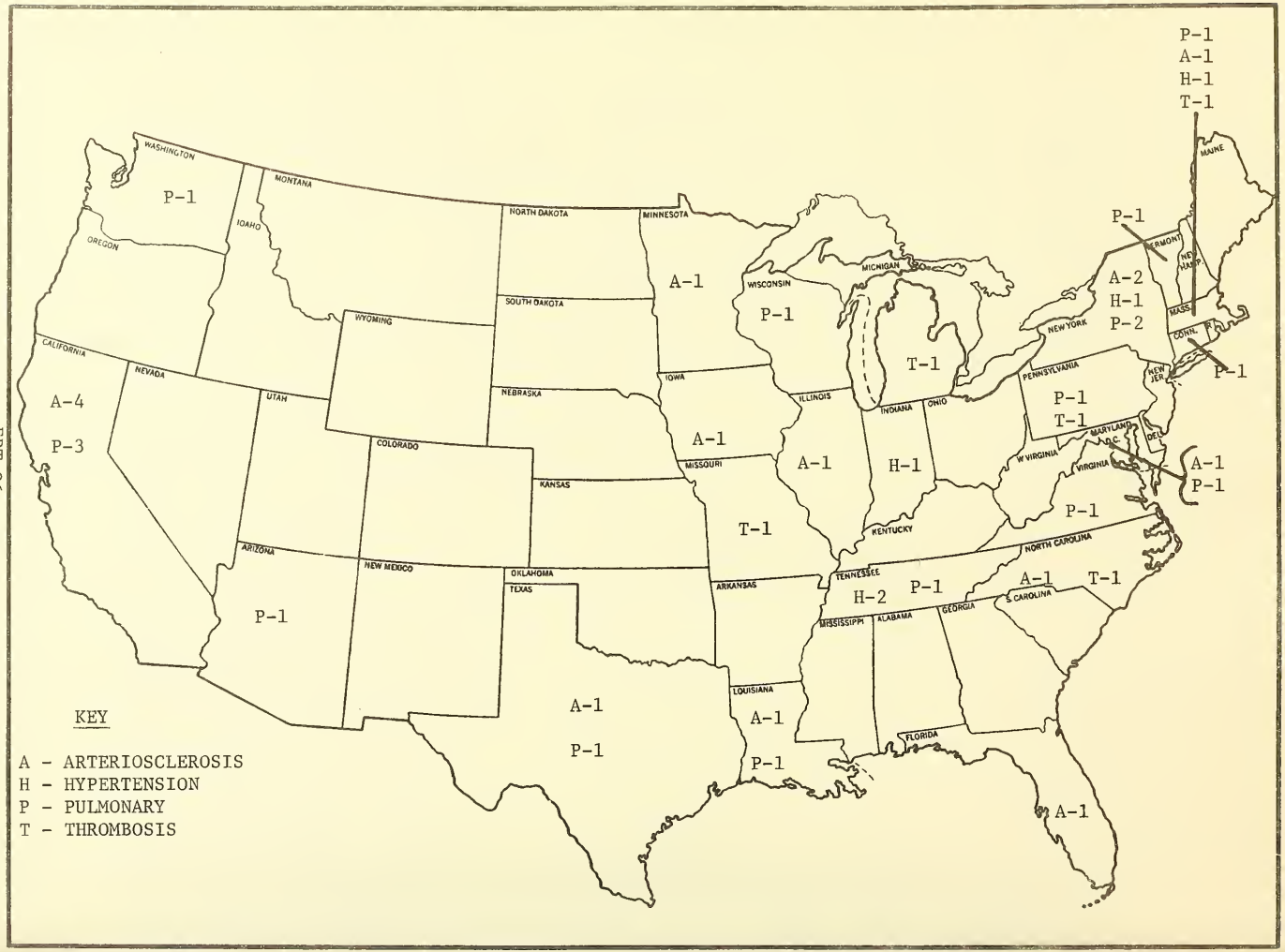
During fiscal year 1971 the Institute launched a new and special kind of grant program in four disease areas. These Specialized Centers of Research (SCOR) were established to focus resources, facilities, and manpower on certain high-priority problems in arteriosclerosis, pulmonary diseases, thrombosis, and hypertension. During that year 34 Center grants were awarded for a total of $16.4 million. During fiscal year 1972 another competition was announced but this was limited to the arteriosclerosis and pulmonary disease areas. A total of 53 valid applications were received and reviewed and, at a special meeting of the Advisory Council, 8 new Centers were favorably recommended--6 in pulmonary diseases and 2 arteriosclerosis. The geographic distribution of all 42 Specialized Centers is shown in the accompanying map.

As anticipated, there is a somewhat uneven distribution across the continental United States; it should be noted that geographic considerations were not one of the critera utilized by the reviewers or the Institute staff. In this SCOR Program a unique relationship exists among the Centers in each disease area and, as well, between the Centers and the Institute's scientific staff. This is a grants program that is focused and represents a cooperative venture on the part of the Institute's staff and the staff of the Centers.

The Training Programs represent the Institute's most obvious investment in the future. As can be seen from Table III the total training activity in fiscal year 1972 totaled approximately $25 million. Most of this is represented by grants to institutions and it should be noted that the size and scope of this program has not expanded significantly in recent years; the Institute is supporting fewer training programs in 1972 than it did in 1971 or even 1965. Furthermore, the Institute has not been able to keep pace with the increasing cost of complex modern instruction, rising tutition fees, house staff salary levels and other inflationary costs. In particular, the NIH stipend level for trainees is deemed to be grossly inadequate.

NHLI undergraduate training grants have been awarded for many years to virtually all of the medical schools to develop and improve their teaching program for medical students. These grants terminate in fiscal year 1972. A similar effort to develop the medical school curriculum in lung diseases is urgently required and a modest start in this direction has been made--the Pulmonary Academic Awards. As indicated in the Table the Institute will have a total of 16 Pulmonary Academic Awardees this year.

The final Table displays some data concerning the staffing pattern of the Extramural Programs during the last 12 years and also indicates the number of grants and awards and budget levels. It is abundantly clear that the full impact of the programmatic reorganization of the Extramural Division has not been realized because the number of qualified scientific and professional staff and supporting staff has not kept pace with the increasing responsibilities of the Division. Indeed, the recruitment of adequate numbers of well-trained, competent staff represents the most crucial and urgent problem facing our Extramural Programs. It continues to hamper our efforts to achieve the ultimate control and prevention of cardiovascular, pulmonary, and blood diseases that remain this nation's number one health problem.


P-1
A-1
H-1
T-1
WASHINGTON
P-1
OREGON
CALIFORNIA
A-4
P-3
NEVADA
IDAHO
MONTANA
WYOMING
UTAH
ARIZONA
P-1
COLORADO
NEW MEXICO
NORTH DAKOTA
SOUTH DAKOTA
NEBRASKA
KANSAS
OKLAHOMA
TEXAS
A-1
P-1
MINNESOTA
A-1
IOWA
A-1
MISSOURI
T-1
ARKANSAS
LOUISIANA
A-1
P-1
WISCONSIN
P-1
MICHIGAN
T-1
ILLINOIS
A-1
INDIANA
H-1
OHIO
KENTUCKY
TENNESSEE
H-2
MISSISSIPPI
ALABAMA
GEORGIA
FLORIDA
A-1
S CAROLINA
P-1
NORTH CAROLINA
P-1
A-1
T-1
VIRGINIA
A-1
P-1
W VIRGINIA
MARYLAND
D.C.
DEL.
PENNSYLVANIA
P-1
T-1
NEW YORK
A-2
H-1
P-2
NEW JER.
P-1
CONN.
MASS.
VERMONT
NEW HAMP.
MAINE
P-1
KEY
A - ARTERIOSCLEROSIS
H - HYPERTENSION
P - PULMONARY
T - THROMBOSIS

NHLI RESEARCH GRANTS AWARDED BY PROGRAM BRANCH

(RESEARCH GRANTS AND PROGRAM PROJECTS)

	1970		1971		1972	
	$	%	$	%	$	%
Arteriosclerotic Disease	$14,234,160	16.4	$22,001,967	20.3	$24,066,329	19.8
Cardiac Disease	19,624,608	22.7	20,432,789	18.9	23,412,522	19.3
Pulmonary Disease	5,594,436	6.5	11,216,791	10.3	13,781,670	11.3
Hypertension & Kidney	11,132,410	12.9	14,689,706	13.5	14,764,539	12.2
Special Programs Branch	18,983,421	21.9	19,656,653	18.1	22,500,047	18.6
Therapeutic Evaluations	5,548,034	6.4	5,765,006	5.3	5,894,806	4.9
Thrombosis & Hemmorrhagic Diseases Branch	11,437,935	13.2	14,881,088	13.6	16,836,909	13.9
TOTAL	$86,555,004	100	$108,644,000	100	$121,256,822	100

TABLE I

NHLI-ERT
RESEARCH GRANTS BY BRANCH
FY 1972

Branch	Amount Awarded	% of ERT $	# of Grants	% of ERT Grants
Arteriosclerotic Diseases				
Arteriosclerosis	$15,011,689	12.4	146	9.5
Cerebrovascular Disease	409,504	0.3	11	0.7
Coronary Heart Disease	6,861,258	5.6	69	4.5
Peripheral Vascular Disease	1,427,943	1.2	30	1.9
Other (Aging & C-T)	355,935	0.3	5	0.3
Total	$24,066,329	19.8	261	16.9
Cardiac Diseases				
Cardiac Arrhythmias	2,513,374	2.1	62	4.0
Cardiac Diseases	4,406,499	3.6	49	3.2
Cardiovascular Dynamics	8,814,679	7.3	170	11.1
Heart Failure & Shock	5,281,737	4.3	117	7.6
Congenital & Rheumatic Heart Dis.	2,396,233	2.0	34	2.2
Total	$23,412,522	19.3	432	28.1
Hypertension & Kidney Diseases				
Hypertension	9,311,912	7.7	132	8.6
Kidney & Body Fluids	5,452,627	4.5	76	4.9
Total	$14,764,539	12.2	208	13.5
Pulmonary Diseases				
Pulmonary Disease	13,781,670	11.3	183	11.9
Infection	-	0.0	-	0.0
Total	$13,781,670	11.3	183	11.9
Thrombosis & Hemorrhagic Diseases				
Blood Components & Diseases	16,286,776	13.4	259	16.8
Hepatic Diseases	346,596	0.3	9	0.6
Reticuloendothelial System	203,537	0.2	5	0.3
Total	$16,836,909	13.9	273	17.7
Therapeutic Evaluations	5,894,806	4.9	79	5.1
Special Programs				
Artificial Heart	3,899,615	3.2	27	1.8
Multicategorical	16,104,413	13.3	27	1.8
Transplantation	1,212,108	1.0	20	1.3
Other	1,283,911	1.1	29	1.9
Total	$22,500,047	18.6	103	6.8
Grand Total	$121,256,822	100.0	1539	100.0

TABLE II

NHLI EXTRAMURAL TRAINING FUNDS (IN MILLIONS)

	1965		1971		1972	
	#	$	#	$	#	$
GRANTS TO INSTITUTIONS						
Undergraduate	105	2.4	115	2.7	114	2.7
Graduate	283	13.0	253	13.8	243	15.6
TOTAL	388	15.4	368	16.5	357	18.3
AWARDS TO INDIVIDUALS						
Research Fellowships	299	2.9	168	2.0	139	1.4
Research Career Development Award	130	2.3	152	3.8	126	3.6
Pulmonary Academic Award	-	-	4	.2	16	.7
Research Career Award	41	1.0	26	.8	26	.9
TOTAL	470	6.2	350	6.8	307	6.6

TABLE III

NHLI EXTRAMURAL PROGRAMS
COMPARISON OF STAFFING, GRANT AND BUDGET
LEVELS 1960 - 1972

	1960	1965	1970	1972
STAFF				
Scientific Professional	14	24	15	20
Supporting	48	79	56	56
TOTAL	62	103	71	76
NUMBER OF GRANTS AND AWARDS				
Research	1873	2234	1571	1539
Training	309	388	360	357
Fellowships	533	470	363	307
TOTAL	2715	3092	2294	2203
TOTAL FUNDS OBLIGATED (MILLIONS)				
Research	$40	$85	$86	$121
Training	10	15	17	18
Fellowships	2	7	7	7
TOTAL	$52	$107	$110	$146

TABLE IV

DATE DUE

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